CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206143Orig1s000

MEDICAL REVIEW(S)

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: March 24, 2015

From: Stephen M. Grant, M.D.
Deputy Director
Division of Cardiovascular and Renal Products /CDER

To: Ellis Unger, M.D.
Director
Office of Drug Evaluation 1 /CDER

Subject: Indication statement proposed for the ivabradine label

Introduction

Amgen has submitted NDA 206143 seeking approval to market ivabradine for treatment of patients with heart failure and reduced ejection fraction on maximally tolerated doses of beta-blockers. Reviews of the NDA have been submitted by Drs. Dunnmon and Beasley (clinical; 4 Dec 2014), Dr. Bai (biostatistics; 17 November 2014), Dr. Marciniak (CDTL; 8 December 2014 *et al*), and Dr. Stockbridge (Division; 4 March 2015). The review team supports approval and you have indicated that you plan to approve.

A draft label was sent to the applicant on 20 March with the following proposed language for section 1:

INDICATIONS AND USAGE

TRADENAME (ivabradine) is indicated for the treatment of patients with stable, symptomatic (b) (4) chronic heart failure with reduced left ventricular function (left ventricular ejection fraction ≤ 35%), who are in sinus rhythm with resting heart rate ≥ 70 beats per minute on maximally tolerated doses of beta blockers. (b) (4)

I believe this is not a clear or accurate description of the benefit ivabradine conveys. Describing the results of the trials of ivabradine accurately is important because prescriber decisions are likely to (and should) differ if ivabradine has been shown to reduce the risk of death and of hospitalization as opposed to reducing only the risk of hospitalization. I have proposed as an

alternative the following:

> TRADENAME (ivabradine) is indicated for the treatment of patients with stable, symptomatic [redacted] (b) (4)) chronic heart failure caused by reduced left ventricular function and who are in sinus rhythm with resting heart rate ≥ 70 beats per minute on maximally tolerated doses of beta blockers. [redacted] (b) (4)

I am not formally a member of the review team for this NDA but I am involved in my position as Deputy Division Director and have worked on various CDER initiatives related to labeling, in particular those related to indication statements. I have stated my views about the indication to both you and Dr. Stockbridge in informal conversation and email exchanges over the past few months but a rationale for the proposed indication has not yet been provided. In an email on 20 March 2015 you indicated that you did not object to my documenting my concerns in the administrative record.

Background

Ivabradine lowers the heart rate by inhibiting the cardiac ion channel (I_f) that regulates spontaneous depolarization of the sinus node. Servier conducted two outcome trials of ivabradine in patients with heart failure (Amgen obtained the rights to ivabradine after both trials had completed and been reported; in fact after approval for this indication in the EU). Both trials were conducted wholly outside the United States (OUS) not under IND and the dates of conduct overlapped.

In the first trial, BEAUTIFUL, stable patients with coronary artery disease and left-ventricular ejection fraction of < 40% who were 55 years or older and in sinus rhythm with resting heart rate (HR) ≥ 60 beats per minute (bpm) were randomized 1:1 to ivabradine titrated to a maximal dose of 7.5 mg bid versus placebo on a background of conventional therapy. Most patients (87%) were on beta-blockers, most patients (65%) had left ventricular ejection fraction (LVEF) ≤ 35%, and most patients (85%) had New York Heart Association (NYHA) class 2 or 3 heart failure symptoms (although patients were not required to have symptoms of heart failure to be eligible to enroll). The mean HR was 72 bpm and 49% of subjects had a baseline HR < 70 bpm. Subjects were administered 5 or 7.5 mg ivabradine bid; the mean dose of ivabradine administered was 6.2 mg bid. The primary analysis was time to the first occurrence of either cardiovascular (CV) death or hospitalization for acute myocardial infarction or hospitalization for new-onset or worsening heart failure (WHF). The trial was not successful; hazard ratio 1.00 (95% CI = 0.91, 1.10). CV mortality trended adversely; hazard ratio 1.07 (95% CI = 0.91, 1.10).

In the second trial, SHIFT, stable patients with at least NYHA class 2 symptoms of heart failure in sinus rhythm with resting HR ≥ 70 bpm and left-ventricular ejection fraction of ≤ 35% were randomized 1:1 to ivabradine titrated to a maximal dose of 7.5 mg bid versus placebo on a background of conventional therapy including maximally tolerated doses of beta-blockers. The etiology of HF in most subjects (68%) was coronary artery ischemia. Most patients (89%) were taking beta-blockers, but only about 20% were on guideline-defined target dose. Subjects were administered 2.5, 5, or 7.5 mg ivabradine bid; the mean dose of ivabradine administered was 6.4 mg bid. The primary analysis was time to the first occurrence of either cardiovascular death or hospitalization for worsening heart failure. The trial was successful; hazard ratio 0.82 (95% CI =

0.75, 0.90; p-value < .0001). As first events, there were fewer hospitalizations for WHF in subjects randomized to ivabradine (505 vs. 660) but more CV deaths (288 vs. 277). However in the overall trial cardiovascular mortality trended favorably; hazard ratio 0.91 (95% CI = 0.80, 1.03; nominal p-value ~ 0.13).

AMGEN has indicated that the primary support for the indication they are seeking is derived from SHIFT with BEAUTIFUL providing supportive evidence for safety analyses. The clinical reviewers of this NDA, the CDTL, and the Division director all support approval, reasoning that the evidence of efficacy demonstrated in SHIFT is strong enough to support approval based on a single trial. The statistical reviewer did not explicitly opine on approvability but was concerned about BEAUTIFUL's lack of success

Ivabradine's Effect on Mortality

No one on the review team has asserted that there is substantial evidence that ivabradine reduces mortality in the population for which it is intended. The clinical reviewers and the CDTL concluded that a mortality effect was suggested in a subpopulation identified *post hoc*, which implies they do not believe there is a mortality effect in the overall population. The clinical reviewers concluded that ivabradine reduced mortality in patients who cannot tolerate beta-blockers with heart rates ≥ 75 bpm and the CDTL concluded that it did so in yet another subpopulation, patients taking a loop diuretic. The statistical reviewer did not explicitly opine but his concern about the directionally different result in BEAUTIFUL suggests he does not believe that an effect on mortality has been demonstrated. The Division Director did not directly address the issue in his memo. Hence I believe the reviewers of this NDA have more or less reached consensus that ivabradine has not been demonstrated to reduce mortality in the indicated population.

I will not address the question of whether the indication should state that ivabradine reduces mortality in a subpopulation identified *post hoc*. If a subgroup analysis is not specified as a secondary endpoint as part of a plan for preserving alpha, it is not possible to limit the probability of accepting a *post hoc* subgroup finding as true despite being spurious. Occasionally, after careful consideration, these exploratory analyses are discussed in the Clinical Studies section of a drug label in an attempt to provide the best possible description of the trial results. But they usually are not included in the indication statement, where the benefit stated is required to meet the substantial efficacy standard.

I also believe there is considerable uncertainty about the effect of mortality in the indicated population. Because the reviews did not explicitly address the question, I will discuss the reasons for my conclusion below.

In SHIFT, the hazard ratio for CV death was 0.91 with a nominal p-value ~0.13 and so the finding does not meet conventional threshold for statistical significance. Because CV death is a component of a composite endpoint, the p-value may not be the only consideration in determining if there is an effect and we do not generally require that all components of a composite be statistically significant at $p < 0.05$ to conclude there was an effect on a component. However, certain composites have components which share a similar pathophysiology leading to confidence that an effect on the composite is likely the result of an effect on all the components.

For example, the composite endpoint of CV death, stroke, MI is commonly used in trials of antithrombotic drugs in CAD patients because all the components are the result of thrombotic events and so an antithrombotic should affect all of them. The composite in SHIFT does not have this characteristic. It is not clear that a drug with an effect on the reversible morbidity of hospitalization should be expected to also improve survival. There are drugs that decrease HF hospitalization and yet are either proven not to improve survival or are not known to have an effect on survival. In the DIG trial in which patients with HF were randomized to digoxin or placebo, digoxin decreased the rate of hospitalization for WHF [risk ratio, 0.72; (95% CI 0.66, 0.79; nominal p <0.001)] but had no effect on CV mortality [risk ratio, 1.01; (95% CI 0.93, 1.10)]. (b) (4) And finally inotropes such as amrinone and dopamine acutely improve the symptoms of heart failure but increase mortality. Hence I conclude that for some drugs the effect in patients with HF on hospitalization for WHF may differ significantly from those on CV mortality and so ivabradine's failure to demonstrate a significant effect on mortality in SHIFT warrants further consideration.

SHIFT was conducted entirely OUS and patients were not treated in a manner consistent with American standards of practice. In particular, the percentage of subjects treated with beta-blockers at doses consistent with current ACC/AHA guidelines was quite low (26%). Both beta-blockers and ivabradine have effects on lowering heart rate and the effect of both on outcomes in patients with heart failure is thought to be caused mostly by that mechanism. The clinical reviewers include in their review an analysis of the primary endpoint which demonstrates a graded effect of beta-blocker dose on outcome with no effect of ivabradine in patients on guideline-defined target doses of beta-blockers but a large effect on patients not on beta-blockers. I think it is a reasonable assumption based on the mechanism of action of beta blockers and ivabradine and the clinical reviewers' analysis that there is an interaction between beta blocker dose and the effects of ivabradine. So in a population more intensively treated with beta-blockers the benefit of ivabradine is likely diminished.

Similarly insertion of an ICD is an ACC/AHA guideline class 1A indication for patients with EF < 35% and class 2-3 symptoms because multiple randomized controlled trials have demonstrated a 25-30% reduction in mortality. In SHIFT virtually all subjects met the criteria for an ICD but the rate of ICD use was only ~ 3%. That rate is far below American norms as evidenced by the recent report of the (b) (4) It may be relevant that ivabradine's effect on mortality was primarily on 'HF death' and not sudden death because the effect of ICDs is mostly prevention of sudden death. So the concern about an interaction between the two therapies is less compelling than for beta-blockers. However determining whether a death is a HF death or sudden death can be difficult so interaction between the effects of ICDs and ivabradine cannot be excluded. The large difference in use of ICDs at a minimum supports the notion that the SHIFT population is different from American patients because of the less intense use of therapies proven to reduce mortality.

Most important, however, is that a trial, BEAUTIFUL, enrolling a similar population and dosing ivabradine similarly to that administered in SHIFT did not reduce CV death. The HR for CV

mortality in BEAUTIFUL was 1.07; i.e. CV mortality in BEAUTIFUL trends negatively to about the same degree as SHIFT trends positively. I believe that the two trials are similar enough that had they both been successful at a marginal p-value (i.e., ~ 0.05), the Division would have accepted that one supported the other for demonstration of safety and efficacy and so both should be considered when making major decisions about efficacy and safety.

However, SHIFT and BEAUTIFUL were not identical trials; patients with lower HRs could enroll in BEAUTIFUL, patients in BEAUTIFUL did not have symptoms of HF (although they had heart failure according to currently accepted classifications), and patients with a slightly higher EF could enroll in BEAUTIFUL. Of these differences I believe that only the differences in baseline HR could be significant. 85% of the subjects in BEAUTIFUL had class 2 or 3 HF symptoms. Determination of LVEF by echocardiography is imprecise with an interindividual and intraindividual variation of at 5 - 10%. Further, even if LVEF could be measured more precisely, measurement of LVEF is a continuous variable and small differences have not been observed to have large effects on HF outcomes. The baseline HR of about half the subjects in BEAUTIFUL was below the minimum required to be eligible to enroll in SHIFT - 70 bpm). Because ivabradine's mechanism of action is reduction in HR, it is reasonable to think its benefit may be attenuated or it may even be harmful in patients with lower heart rates. However, CV mortality in subjects whose baseline HRs were ≥ 70 bpm [hazard ratio 1.02 (95% CI = 0.86, 1.21)] was not significantly different from CV mortality in all subjects enrolled in BEAUTIFUL.

There have been various attempts to analyze outcomes among the patients in BEAUTIFUL who were "SHIFT-like." I believe everyone has lost enthusiasm for these analyses because the outcome hinges on the definition of "SHIFT-like" patients and that cannot be done because it is not clear precisely which make a subject "SHIFT-like." And generally *post hoc* analyses of unsuccessful trials made with data in hand should be viewed with suspicion because of the impossibility of knowing whether the analyses were shaped to get the result desired (a statement that applies to FDA *post hoc* analyses as well as those from applicants).

Description of Ivabradine's Benefit in the Indications and Usage Section of the Label

If you agree that there is not substantial evidence that ivabradine reduces the risk of CV death in the indicated population, the question then becomes how to describe the benefit provided by ivabradine in the indicated population for health care practitioners and patients. The reviews completed thus far do not explicitly consider the question. The Division Director in his memo dated 4 March 2015 states he believes the indication should be approximately as stated in the draft label quoted above. However he does not provide a rationale for his preference nor discuss the situation in any detail.

Part of the issue here is whether it is appropriate to decompose a composite primary endpoint to try to identify the effects on individual components. In a statistical sense, the drug is only proven to have an effect on the composite and not on the individual components (unless the analysis plan specifies a component or components as formal secondary endpoints within a plan to conserve alpha). And one can never be sure of the magnitude of effect on individual components of a composite endpoint if occurrence of one of the components affects the occurrence or likelihood of observing the occurrence of other components but of course that is not a problem for mortality. Nonetheless, the Division has not consistently included all the

components of a composite endpoint in section 1 of the PI. For example the results of LIFE, a study of the effect of losartan vs. atenolol on the composite of CV death, stroke and MI in patients with diabetes, hypertension, and left-ventricular hypertrophy, are displayed in the label as follows:

	Losartan		Atenolol		Risk Reduction	95% CI	p-value
	N (%)	Rate	N (%)	Rate			
Primary Composite Endpoint	508 (11)	23.8	588 (13)	27.9	13%	2% to 23%	0.021
Components of Primary Composite Endpoint (as a first event)							
Stroke (nonfatal)	209 (5)		286 (6)				
MI (nonfatal)	174 (4)		168 (4)				
Cardiovascular mortality	125 (3)		134 (3)				

The indication does not reflect the composite primary endpoint but states "COZAAR is indicated to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy," i.e. states the expected benefit is confined to just one of the three components of the composite primary endpoint.

A more recent example is cangrelor. The primary endpoint of the principal trial providing evidence of safety and effectiveness was a composite of death, MI, stent thrombosis, and ischemia driven revascularization. The number of deaths was the same in patients randomized to cangrelor and control. At the meeting of the Cardiovascular and Renal Drug Advisory Committee held on 12 February 2014 the applicant requested an indication for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients undergoing percutaneous coronary intervention; i.e., the applicant recognized that a mortality claim could not be sustained. Therefore it appears to me that the Agency has exercised discretion at times in the past in describing the benefit in the indication and has not always included all components of a composite primary endpoint.

Further recent initiatives to improve the Indications and Usage section of labels should be considered. It has been emphasized that the purpose of labeling is to enable health care practitioners to readily identify appropriate therapies for patients by clearly communicating the drug's approved indication, i.e. the indication should unambiguously state the benefits expected in the intended population if they take the drug. To this end we have been encouraged to clearly and concisely convey the use(s) for which the drug has been shown safe and effective using terminology that is understandable to health care practitioners and which will facilitate the ability to index the indication(s) in electronic drug databases. (b) (4) But I believe that point is likely to be lost on many health care practitioners who are not as familiar with labeling/statistical nuance as some Agency personnel. There is substantial evidence that ivabradine reduces the rate of hospitalization for worsening heart failure. There is not substantial evidence that ivabradine reduces CV mortality; in fact there is considerable uncertainty about its effect on mortality. So the indication should state that ivabradine reduces the risk of hospitalization for WHF and be

silent about its effect on CV mortality. Discussion of the composite primary endpoint and description of the observed results for each component belong in the Clinical Trials section.

Finally, the final sentence, which states (b) (4) is factually incorrect or, at least, ambiguous. The treatment effect as assessed by the effect on the primary endpoint was solely the result of a reduction in hospitalization for WHF; as a first event more ivabradine subjects died of CV causes.

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/s/

STEPHEN M GRANT
03/24/2015

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Divisional Memo

NDA: 206143 Ivabradine (Corlanor) for heart failure.

Sponsor: Amgen

Review date: 4 March 2015

Reviewer: N. Stockbridge, M.D., Ph.D.
Steven Bai, Ph.D.

This memo conveys the Division's recommendation to issue an "Approval" letter for this application. The application was granted a priority review, but the clock was extended.

Reviews I reference are as follows:

Discipline	Reviewers	Date	Summary	Pages
CMC	Wilson-Lee	2 December 2014	Primary review	74
	Suarez	21 November 2014	Biopharmaceutics	26
Nonclinical	Wu	18 November 2014	Carcinogenicity	36
		19 November 2014	Genotoxicity	42
		25 November 2014	Reproductive and developmental toxicology	55
		28 November 2014	Overall	266
Clinical pharmacology and pharmacometrics	Sahre Sabarinath	26 November 2014	Primary review	32
Clinical	Dunnmon Beasley	4 December 2014	Primary review	232
Statistics	Bai	17 November 2014	Primary review	26
CDTL	Marciniak	8 December 2014	Review memo ·Actual CDTL memo ·Memo on spironolactone and related trials ·2012 Analysis plan for ARBs and cancer ·CDTL memo for Ranexa	171 (56) (22) (57) (37)
		17 December 2014	Cancer risk memo ·Ivabradine ·Antiplatelets and anticoagulants ·Slides from DAPT ·2013 ARBs ·2012 Analysis plan for ARBs and cancer	351 (3) (63) (187) (42) (57)
		18 December 2014	Summary of issues	29
		19 December 2014	Financial disclosure	5

The CMC reviews were not covered in the CDTL review. There are no CMC issues with either 5- or 7.5-mg tablets, and shelf-life is 24 months for the bottles and 36 months for the blisters. Facility inspections are complete and rated acceptable.

Ivabradine is highly soluble in water, so a disintegration test is used in lieu of dissolution. Testing methods and criteria are agreed; there are no unresolved biopharmaceutics issues.

Genotoxicity risk was considered unlikely. There were no findings of concern in 2-year carcinogenicity studies in mice and rats.

There were no effects of concern on reproduction in the rat. There were teratogenic findings in the rat (ossification defects, gross malformations to heart and major vessels at small multiples of human exposure), but not in the rabbit. I do not know which result is likely to pertain to humans.

Ivabradine inhibits I_f, the major pacemaker current, in nodal pacemaker cells and, with similar affinity, a similar current in the retina. The former reduces heart rate, the mechanism by which one supposes the benefits are derived. The latter is likely to be responsible for reversible visual disturbances in man. At doses producing about the same exposure as in man, rats, but not dogs, get myocardial degenerative findings similar to what is seen with beta blockers in rodents.

In man, absolute bioavailability is about 40%, limited by first-pass metabolism, principally CYP3A. Exposure increases linearly with dose. Ivabradine and its main metabolite are about equally active. Peak levels of ivabradine appear within an hour. The kinetics are monophasic with a half-life of 2-3 h after a single dose or about 3-4 h after multiple dosing. The volume of distribution is about 100 L; about 70% is protein-bound, mostly to albumin. Various metabolites are excreted in urine and feces. Severe renal impairment and moderate (worst studied) hepatic impairment alter PK little. Strong and moderate 3A4 inhibitors were banned from clinical studies, as were other negative chronotropes, verapamil and diltiazem, but not beta-blockers.

Ivabradine potently inhibits the renal OCT2 transporter. OCT2 substrates, like metformin, were not banned from SHIFT, and a dedicated drug interaction study revealed no material effect on exposure (Cmax or AUC) to metformin. I am a little puzzled by the lack of effect.

The clinical review lays out the background well. Heart failure with reduced ejection fraction is common and associated with high morbidity and mortality, despite approved therapy with RAAS blocker, beta-blockers, diuretics, aldosterone antagonists, and implantable defibrillators.

Ivabradine is approved in EU for angina and heart failure. All studies were conducted outside a US IND. Years after completion of SHIFT (2006-2010), Servier attempted to collect financial disclosure information and succeeded with about half the study sites accounting for about half of the enrollment. Analysis of results by disclosure status raises no concern, and I believe a good faith effort was made to provide information.

The primary basis for the claim is SHIFT, a study conducted in patients with stable NYHA II-IV heart failure, hospitalized within the past year, with EF<35% and in normal sinus rhythm with heart rate >70 bpm. Subjects were randomized to study drug or placebo and followed until there were 710 events. The primary end point was time to first adjudicated CV death or hospitalization for worsening heart failure. Results[1] for

[1] *The only statistical concern was the late finalization of the statistical analysis plan. After BEAUTIFUL failed, the sponsor increased the target number of events in SHIFT from 1220 to 1600, but by this time the p-value (Bai;*

the primary end point, components thereof, and the secondary end points are described below:

	Placebo N=3264	Ivabradine N=3241	HR (95% CI)	P
CV death or HWHF	28.7%	24.5%	0.82 (0.75, 0.90)	<0.0001
CV death	15.0	13.9	0.91 (0.80, 1.03)	0.13
Hosp for WHF	20.6	15.9	0.74 (0.66, 0.83)	<0.0001
All-cause death			0.90 (0.80, 1.02)	NS[2]
Heart failure death			0.74 (0.58, 0.94)	
All-cause hosp			0.89 (0.82, 0.96)	
CV hospitalization			0.85 (0.78, 0.92)	

Analyses excluded 46 subjects at two Polish sites and 7 subjects who did not meet entry criteria and were never dosed. How these are handled in the analyses cannot possibly matter.

"Supportive" data came from BEAUTIFUL (2004-2008), a study conducted in patients with left ventricular dysfunction (but not necessarily heart failure), stable coronary artery disease, and resting heart rate >60 bpm. Subjects were randomized to study drug or placebo. The primary end point was time to first adjudicated CV death or hospitalization for heart failure or for MI. Results for the primary end point and for components thereof are described below:

	Placebo N=5438	Ivabradine N=5479	HR (95% CI)	P
CV death, HWHF, MI	15.3%	15.4%	1.00 (0.91, 1.10)	0.95
CV death	8.0	8.6	1.07 (0.94, 1.22	0.32
Hosp for HF	7.9	7.8	0.99 (0.86, 1.13)	0.85
MI	4.2	3.6	0.87 (0.72, 1.06)	0.16

If you take BEAUTIFUL subjects with NYHA II-III and HR >70 bpm, the results look much more similar to the overall BEAUTIFUL results than they do to SHIFT:

	Placebo N=1679	Ivabradine N=1684	HR (95% CI)	P
CV death or HWHF	19.8%	18.7%	0.93 (0.80, 1.08)	
CV death	11.5	11.8	1.03 (0.84, 1.24)	
Hosp for WHF	12.8	11.7	0.90 (0.74, 1.10)	

…but if you further select to match EF, heart rate, and history of MI, the results are less inconsistent with SHIFT:

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page 15) was well under 0.05 where it remained. However, the only version of the SAP appears to be the one dated after the last subject was enrolled but before unblinding.

[2] It is probably generally not a good idea to put all-cause mortality into an alpha-conserving statistical plan, since there is no "all-cause" claim. However, the next logical assessment is the "CV death" component of the primary end point, and the null hypothesis there was not rejected either. Therefore, I do not think there is an adequate basis to include any mortality result among the study's reliable findings.

	Placebo N=611	Ivabradine N=592	HR (95% CI)	P
CV death or HWHF	24.7%	19.6	0.77 (0.60, 0.98)	
CV death	14.2	13.0	0.91 (0.67, 1.24)	
Hosp for WHF	17.0	12.3	0.70 (0.52, 0.94)	

Also noteworthy is SIGNIFY (2009-2014), a study in patients with coronary artery disease, as evidenced by MI more than 3 months ago, EF >40% (i.e., this population does not overlap at all with the SHIFT inclusion criteria), documented multi-vessel disease or single vessel disease with a positive stress test or unstable angina, and at least two other risk factors. Subjects were randomized to study drug or placebo. The primary end point was time to first CV death or nonfatal MI. Results for the primary end point and for components thereof are described below:

	Placebo N=9552	Ivabradine N=9550	HR (95% CI)	P
CV death, MI	6.4%	6.9%	1.08 (0.96, 1.20)	0.35
CV death	3.2	3.5	1.10 (0.94, 1.28)	
MI	3.6	3.7	1.04 (0.90, 1.21)	

Clinical and clinical pharmacology reviewers openly support approval, as does the CDTL. The statistical review has no recommendation. Various issues—discussed at extraordinary length in these reviews—concern to whom the observed results apply.

The simplest such issue concerns the discrepant results among SHIFT, BEAUTIFUL, and SIGNIFY. All had similar end points, but different populations. SHIFT enrolled subjects with manifest heart failure, reduced EF, and recent heart failure hospitalization. BEAUTIFUL enrolled subjects with coronary artery disease and generally less left ventricular dysfunction. I do not take a lot of support from the BEAUTIFUL subgroup that looks most like the SHIFT population, but the results are generally consistent with SHIFT. Subjects in SIGNIFY had coronary disease but EF >40%, so they overlap not at all with those in SHIFT. As one shifts away from the SHIFT demographic, ivabradine works progressively less well. These trials are different enough in whom they were conducted that I do not find their results inconsistent, nor do I find their discrepancies troubling to interpret.

Various subset analyses have been explored in SHIFT, and then the other studies have been explored for confirmation. I will address these in what follows.

The analyses of the primary end point by pre-specified subgroups are shown below[3]:

[3] *Figure is from the sponsor's draft labeling* (b) (4)

(b) (4)

No important interactions are seen for the primary end point in SHIFT by sex, age, or race, although there is little experience with ivabradine in non-Caucasians.

There is no US enrollment. The statistical review gives an analysis of the primary end point by country, which reveals no important heterogeneity. Dropping the two largest enrolling countries[4], Ukraine and Russia, over 1400 subjects, still produces a nominally statistically significant result.

It is still reasonable to note differences in SHIFT and US practice. SHIFT recruited patients with some intolerance to beta blockers, so the distribution of beta blockers might not have been much different in the US cohort had the US contributed. And only about 10% of SHIFT was on no beta blocker at baseline, which seems pretty good. In the US, many SHIFT-eligible patients would have had an ICD, but how this might have affected the main CV hospitalization effect is unclear. SHIFT probably looks like no country's typical heart failure population, but I think that the label can adequately describe in whom the study was conducted, and there are plenty in the US who match those characteristics.

The statistical review gives the p-value for the interaction with heart rate as 0.029, undiscounted for the 8 analyses shown, and unadjusted for the other 7 pre-specified factors. A more detailed look at this interaction is shown below[5]:

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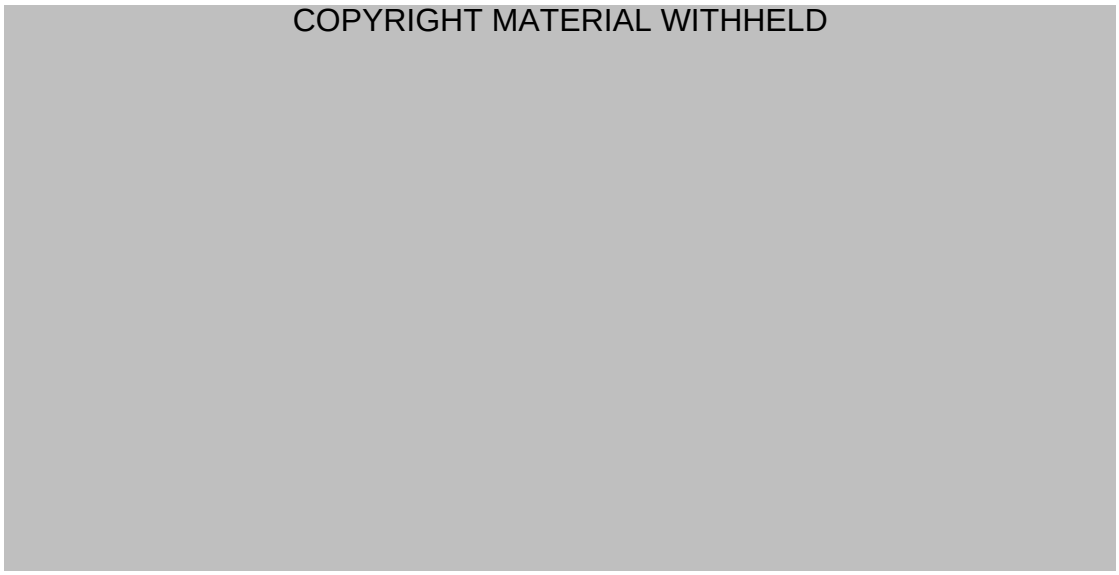
[4] *There is no particular rationale for this assessment, but it did illustrate the robustness of the overall finding.*

[5] *Primary clinical review p 137, attributed to Bohm et al. 2010. Lancet 376:886-894. A similar analysis of the primary end point only appears in the statistical review and Marciniac (8 December 2014) p 28.*



The results suggest a diminished or perhaps no effect at lower heart rates; other cut-point analyses in the reviews gave similar results. The effect by heart rate is probably entangled with effects by beta-blocker use. The reviewers' analyses[6] of the primary end point and both components show graded responses by beta-blocker dose:

	Ivabradine	Placebo	HR (95% CI)	P-value
	n (%)	n (%)		
Primary Endpoint				
No BB	101 (29.4)	134 (39.3)	0.68 (0.52, 0.88)	0.003
BB < 25%	148 (30.8)	171 (40.0)	0.74 (0.60, 0.93)	0.008
BB 25% to 50%	204 (26.2)	260 (30.8)	0.81 (0.68, 0.98)	0.029
BB 50% to 100%	181 (21.6)	212 (24.8)	0.84 (0.69, 1.02)	0.077
BB >= 100%	149 (20.1)	150 (20.1)	0.99 (0.79, 1.24)	0.904
Hosp for WHF				
No BB	65 (18.9)	98 (28.7)	0.60 (0.44, 0.82)	0.001
BB < 25%	99 (20.6)	125 (29.3)	0.68 (0.52, 0.88)	0.004
BB 25% to 50%	131 (16.8)	183 (21.7)	0.75 (0.60, 0.93)	0.01
BB 50% to 100%	124 (14.8)	154 (18.0)	0.79 (0.62, 1.00)	0.05
BB >= 100%	89 (12.0)	106 (14.2)	0.84 (0.63, 1.11)	0.21
CV death				
No BB	63 (18.3)	81 (23.8)	0.72 (0.52, 1.00)	0.05
BB < 25%	84 (17.5)	96 (22.5)	0.81 (0.61, 1.09)	0.163
BB 25% to 50%	119 (15.3)	134 (15.9)	0.94 (0.74, 1.21)	0.637
BB 50% to 100%	96 (11.5)	101 (11.8)	0.95 (0.72, 1.25)	0.702
BB >= 100%	80 (10.8)	74 (9.9)	1.08 (0.79, 1.48)	0.646

Given ivabradine's effect is thought to be mediated through its effects on heart rate, I find the interactions by heart rate and beta blocker to be plausible, but one cannot rule out the possibility this is spurious. The clinical reviewers propose to limit use of ivabradine to patients with baseline heart rate >75 bpm (rather than the SHIFT entry criterion of 70 bpm).

Less easy to understand is an interaction by loop diuretic use reported by Dr. Marciniak[7]. His conclusion is that loop diuretic use predicts poor outcomes, that

[6] *Clinical review, p 130.*

[7] *Review of December 8, 2014; p10-25.*

ivabradine without loop diuretics is detrimental, and that use of ivabradine with a loop diuretic is beneficial. In describing how Dr. Marciniak appears to have reached these conclusions, I[8] will enumerate some issues with these analyses.

Dr. Marciniak cites 7 drug classes he considered, the others being beta blockers, mineralocorticoid receptor antagonists, ACE inhibitors, angiotensin receptor antagonists, digoxin, and statins. There appears to have been no adjustment for this multiplicity.

Dr. Marciniak focuses on cardiovascular death, but this was neither the primary end point in SHIFT nor was the effect of ivabradine on it nominally statistically significant in SHIFT (p=0.13). In addition, he analyzes all randomized subjects (i.e., including the disqualified sites), but only the events that were adjudicated "definite". None of these idiosyncratic choices is adequately explained.

Dr. Marciniak confirms the simple model[9] with "comprehensive" log-rank and Cox models[10], having terms for age, a separate term for age >75, sex, NYHA class, LVEF, heart rate, a separate term for heart rate >75, SBP, weight, history of MI, ischemic etiology, baseline creatinine, baseline potassium, a separate term for potassium >5 mEq/L, beta blocker dose above some threshold, loop diuretic use, MRA use, ARB use, ACE inhibitor use, statin use, and digoxin use, plus 13 two-factor interaction terms from the universe of 231 possible such terms[11]. None of these choices is adequately explained.

Although there are standard techniques for selecting which interaction terms to keep or exclude from such a regression model, there is no evidence that Dr. Marciniak used any. There is no documentation of his methods, and, of the 13 interaction terms he incorporated (including loop diuretics), 5 of them have p-values for the interaction that are >0.2.

It is also unclear how Dr. Marciniak picked the main terms to include. He incorporates terms for all of the sponsor's pre-specified subgroups except for diabetes, and then added others.

Dr. Marciniak finds support for interactions with loop diuretics in analyses of CV mortality in BEAUTIFUL (p=0.054) and SIGNIFY (p=0.084), neither of which had nominally significant results for the primary end point, for CV mortality, or for the interaction with loop diuretics.

Dr. Marciniak dismisses the lack of any interaction (p=0.6) of loop diuretics with ivabradine on the component of the primary end point in SHIFT where the treatment effect is most evident—CV hospitalization[12]—because findings on this end point were "not supported by BEAUTIFUL and SIGNIFY", but the same is true for CV mortality. Dr. Marciniak never mentions an analysis of the loop diuretic interaction using the full primary end point.

Dr. Marciniak does not believe the loop diuretic interaction is a reflection of heart failure, because he finds little interaction with other indices of heart failure severity. He

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[8] "I" continues to refer to the Division Director, but the section of this document addressing the loop diuretic interaction is coauthored by Dr. Bai.

[9] Table 5 of page 12.

[10] Tables 11 and 12 on pages 19 and 20.

[11] There are 21 factors named, plus randomized treatment, so there are 22 x 21 / 2 distinct pairs. Each such interaction term can be included or not in the model, so there are $2^{231} \approx 3x10^{69}$ of these. This does not consider the much larger number of possible higher-order interaction terms.

[12] Table 14 on page 24.

acknowledges a poor mechanistic explanation for the loop diuretic interaction, but he is not particularly troubled by this[13].

It does not appear that the statistical reviewer was consulted for analyses of loop diuretic interaction; there is no mention in the statistical review. Dr. Beasley confirmed Dr. Marciniak's analyses, but questioned them, in part, because of multiplicity issues, which Dr. Marciniak did not address.

The interaction with loop diuretics may well be "real", but I do not find the case at all compelling, lacking rationale and being an island in a wide and deep sea of subgroup analyses.

The safety database from SHIFT is 6538 subjects and nearly 12000 patient-years. Between BEAUTIFUL and SIGNIFY, there is another 30000 subjects and 60000 patient-years.

More than 40% of subjects in SHIFT reported serious adverse events. From the clinical review I abstract SAEs with at least 0.5% higher incidence on ivabradine than on placebo. They are atrial fibrillation (3.9% vs. 3.2%), myocardial infarction (3.6% vs 3.1%), and bradycardia[14] (0.6% vs 0.1%). Of these, only the signal for bradycardia is even nominally statistically significant. Atrial fibrillation and myocardial infarction are each slightly less common on ivabradine in BEAUTIFUL[15].

Adverse events with incidence >0.5% more on ivabradine in SHIFT were:

	Placebo	**Ivabradine**
Atrial fibrillation	6.6%	8.2%
Bradycardia/HR decreased	2.2	9.9
Hypertension/BP increased	7.7	8.7
Phosphenes	0.5	2.8
Vertigo	0.5	1.1

Similar trends are seen in BEAUTIFUL for bradycardia and phosphenes, and there is a lesser trend for atrial fibrillation. Other items in the table above are not seen in BEAUTIFUL and are less likely to be reproducible findings.

The phosphene effect is thought to be mediated through a channel in the retina similar to one at which ivabradine acts in the sinus node. The effect is dose-related and fully reversible.

In summary, I believe the findings from SHIFT that ivabradine reduces the combined risk of CV death and hospitalization for worsening heart failure, and that the claim ought to reflect that wording, and not be restricted to hospitalization. Section 14 can make it clear that this was mostly an effect on one component. I believe that the populations in BEAUTIFUL and SIGNIFY are sufficiently different that they do not undermine the interpretation of SHIFT. BEAUTIFUL and SIGNIFY are, however, large enough to merit consideration for inclusion in labeling as constraints on broad use of ivabradine.

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[13] *Page 7: "[K]nowing the mechanism is never a requirement and [is] in this case … completely unnecessary."*

[14] *Symptomatic plus asymptomatic*

[15] *Myocardial infarction rates on placebo and ivabradine were 3.1% and 3.6% for reported SAEs and 4.2% and 3.6% for adjudicated components of the primary end point.*

I find the observations of effect modification by baseline heart rate and by beta-blocker use sufficiently compelling that I would include them in labeling. I would point out that use in patients with low heart rate or on targeted beta-blocker therapy did not seem to benefit, but neither were they harmed.

I find the observation of an interaction with loop diuretics not to be credible, as it is based upon deep dives into subgroups of an end point that had no overall finding. I would make no mention of this in labeling.

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/s/

NORMAN L STOCKBRIDGE
03/04/2015

STEVE G BAI
03/04/2015

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: December 19, 2014

Reviewer: Thomas A. Marciniak, M.D.
Medical Team Leader

NDAs: All (example from NDA 206-143)

Drugs: All

Subject: Financial disclosure inadequacies

In February 2013 the FDA issued an updated Guidance for Clinical Investigators, Industry, and FDA Staff Financial Disclosure by Clinical Investigators. That guidance addresses the Financial Disclosure by Clinical Investigators regulation (21 CFR part 54). As the introduction of the guidance states, that regulation "requires applicants who submit a marketing application for a drug, biological product or device to submit certain information concerning the compensation to, and financial interests and arrangements of, any clinical investigator conducting clinical studies covered by the regulation." Unfortunately the regulation, and hence the guidance, are completely inadequate for determining whether financial conflicts of interest can bias the results of the modern clinical trial, particularly the large, multicenter trials needed for cardiovascular outcome trials. I describe some of the reasons below.

The fundamental limitation of the regulation is that it focuses on a narrow definition of an investigator "who was not a full-time or part-time employee of a sponsor of the clinical study" and "who is directly involved in the treatment or evaluation of research subjects" and it requires disclosure of payments such as equity interests but not the payments for the conduct of the research. The definition of investigator is the major problem with the regulation. Excessive payments for the conduct of the trial could be conducive to biases but I will not discuss the research conduct payments further.

The definition of the investigator excludes many individuals who can bias trial results. These other individuals include the sponsor or contract research organization (CRO) staff who train and monitor the investigators, the sponsor or CRO staff who collect records or assemble packages for central adjudication or image reading centers, the center staff, the sponsor or staff who assemble the datasets and case report forms for analysis, and the academic research organizations (AROs)

who perform other monitoring activities and analyze the data. In fact, these latter individuals have better opportunities for biasing clinical trial results than the investigators. For example, in a large multicenter trial in which any one site enrolls a small fraction of the patients, any individual investigator cannot bias the overall trial results appreciably. Recruiting many investigators to bias the results would be hazardous, increasing greatly the risk of exposure. However, one trusted individual (with an untraceable copy of the randomization list) who controls the transmission of adjudication packages to a central adjudication committee can easily bias the results: For a heart attack endpoint, simple "forget" to forward the test results used to diagnose heart attacks for some new drug patients and ensure that the placebo patients have complete test results. This scenario is not detected by current audit practices and could be undetectable regardless of the audit approach the FDA is able to implement.

While the example of the adjudication package transmitter might not be considered to be a financial disclosure issue, another example may be more obvious: Well paid AROs who analyze the data and, because they are usually from prestigious academic organizations, provide an air of respectability to the study results may have devoted little effort to the validity of the data. A good example is this attestation from the first publication of the rosiglitazone RECORD study:

> "Members of the steering committee (seven academic investigators and one representative of the sponsor) developed the study design, had full access to the interim data, were responsible for the decision to publish the results, and wrote the manuscript. The committee members vouch for the accuracy and completeness of the data reported." (Home, P. D., S. J. Pocock, et al. (2007). "Rosiglitazone evaluated for cardiovascular outcomes--an interim analysis." N Engl J Med 357(1): 28-38.)

However, when the FDA OSI staff interviewed Dr. Pocock, the chief ARO statistician and co-author of the above statement, about his involvement, the following is the summary of his response:

> "With regard to the RECORD data: a. How would you describe the activities you, your staff, or your co-authors have taken to insure the quality of the RECORD data and your analyses thereof? Dr.[redacted] had the full trial database set to recreate the analysis. We had more of a scientific advisory role, not detailed activities in data management."

AROs routinely add an air of respectability at FDA advisory committee meetings while, as the above example demonstrates, providing no real assurance about trial quality.

The Division and Office leadership recently discussed the problems with financial disclosures with regard to a recent NDA submission. I've included the email thread of that discussion as an Attachment. The topic also was discussed at a meeting. However, I fear the net result of the discussion will be no action. The financial disclosure regulation is worse than inadequate: Recent emphasis upon it, e.g., the distribution of a template for reviewers to fill out, provides the appearance of action while accomplishing nothing—just like the rosiglitazone RECORD attestations.

The FDA must revise and tighten the financial disclosure regulation. The integrity of clinical trial results, and hence the integrity of all drug approvals, will remain questionable until these financial disclosure inadequacies—and other clinical trial problems—are addressed completely.

Marciniak, Thomas

From: Unger, Ellis
Sent: Friday, August 01, 2014 10:19 AM
To: Marciniak, Thomas; Dunnmon, Preston; Stockbridge, Norman L; Grant, Stephen
Cc: Temple, Robert
Subject: RE: Lack of Financial Disclosure and Frank Conflicts in SHIFT

As Tom said, **VERY** interesting.

From: Marciniak, Thomas
Sent: Friday, August 01, 2014 9:36 AM
To: Dunnmon, Preston; Stockbridge, Norman L; Grant, Stephen
Cc: Unger, Ellis; Temple, Robert
Subject: RE: Lack of Financial Disclosure and Frank Conflicts in SHIFT

Very interesting that they disclosed. This illustrates how woefully inadequate our financial disclosure regs are because we ordinarily don't even see the financial arrangements for the CROs and AROs. For large multicenter trials the individual sites can't influence the results much while the CROs and AROs (and sponsor monitors) can, yet we require financial disclosures for the former but not for the latter.

Tom

From: Dunnmon, Preston
Sent: Thursday, July 31, 2014 2:02 PM
To: Stockbridge, Norman L; Grant, Stephen; Marciniak, Thomas
Cc: Gershon, Sharon; Dunnmon, Preston
Subject: Lack of Financial Disclosure and Frank Conflicts in SHIFT

Tom, Steve, and Norman,

I want to make you aware of the status of the financial disclosures for the Ivabradine NDA 206143 – there are issues here involving a large number of missing financial disclosures as well as frank conflicts of interest. To put this information in perspective, recall that SHIFT was not executed under an IND, and indeed, FDA did not see or give input into its design. The study enrolled 6558 patients at 628 non-US sites and was completed 10 April, 2010. Accordingly:

- Collection of Certification/Disclosure Forms in compliance with 21 CFR Part 54 were not prospectively acquired
- In April, 2012 (two years after the study was completed) Servier initiated the collection of Certification/Disclosure Forms
- The Financial Disclosure analysis on this retrospectively acquired information (attachment 1) shows that there are some substantial issues here:

    - Lack of disclosure information. The table of sites without documented financial disclosure status is 200 pages long (see attachment 2, Table 3, pages 211-412). I don't have this as a dataset (or at least haven't found it yet), but as you can see from Table 3, it involves a lot of sites who enrolled lot of patients.

    - Non-trial conflicts of interests. Please note see Table 2, attachment 1, and the Excel file attachment 2 that Sharon Gershon was kind enough to share with me. What you can see from the Table 2 of attachment 1 is that there are 43 investigators with disclosable financial interests. The excel file shows the amounts involved for 38 of these instigators – many large, some huge, and some to people with influence over the larger trial. I will call you attention to two of them that are just eye-popping, not just because of the amounts involved, but because these two people were officers of the CROs that

monitored the trials and on committees involved in the conduct of SHIFT (and BEAUTIFUL and SIGNIFY), as follows:

(b) (6) – Amount disclosed: $59,815,750.00 paid for: (b) (6) $4,416.21 (b) (6) $152,846.15 (b) (6) $224,358.52 (b) (6) : $19,483.52 (b) (6) : $924,528.85 (b) (6) $42,630.49 Payment to (b) (6) : $58,447,486.26

(b) (6) - Amount disclosed: $6,498,489.01paid for: (b) (6)).

I bring this up now (early, before our filing meeting) because I know that financial disclosure is important to the agency, and that it is required. What I don't know is if there is a regulation-driven red line across which the lack of financial disclosure, together with these profound conflicts of interest, are simply unacceptable and should result in an RTF action.

Many thanks,
Preston

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THOMAS A MARCINIAK
12/19/2014

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS AND OFFICE OF DRUG EVALUATION I

Memorandum

NDA: 206316 Edoxaban tosylate (Savaysa) and others

Review date: 13 November 2015

From: Norman Stockbridge, M.D., Ph.D., Director, DCaRP
Mary Ross Southworth, Pharm.D., Deputy Director for Safety, DCaRP
Robert Temple, M.D., Deputy Director, ODE-I
Ellis Unger, M.D., Director, ODE-I

Regarding: Potential for anticoagulant, antiplatelet, and angiotensin receptor blocking (ARB) drugs to cause cancer.

On 12 December 2014, Dr. Thomas Marciniak filed a 347-page review to the following applications:

Application	Brand	Drug	Application	Brand	Drug
NDA 009218	Coumadin	Warfarin	NDA 202155	Eliquis	Apixaban
NDA 20839	Plavix	Clopidogrel	NDA 202439	Xarelto	Rivaroxaban
NDA 21686	Exanta	Ximelagetran[1]	NDA 204866	Zontivity	Vorapaxar
NDA 22307	Effient	Prasugrel	NDA 206316	Savaysa	Edoxaban
NDA 22433	Brilinta	Ticagrelor	TSI 1361		Clopidogrel
NDA 22512	Pradaxa	Dabigatran			

In addition to the above applications, the entire 347-page review is appended to a review that Dr. Marciniak filed to NDA 206143 (Corlanor; ivabradine) on 17 December 2014, and elements of this review appear in a review that Dr. Marciniak filed to NDA 207620 (Entresto; sacubitril plus valsartan) on 28 December 2014.

Dr. Marciniak's review concludes that anti-platelet drugs (clopidogrel, prasugrel, ticagrelor, vorapaxar) and newer anticoagulant drugs (dabigatran, apixaban, rivaroxaban, edoxaban) all potentially cause cancer. It also repeats assertions from a previous review that ARBs cause cancer. Before discussing the specific content of his review, let us note some unusual features related to process:

1. With rare exception, Division reviews are performed on assigned work. This review is unusual in that none of the applications to which it was originally filed was assigned to Dr. Marciniak.
2. Most reviews address a specific application before the Agency—a New Drug Application (NDA), a Biologics License Application (BLA), an Investigational New Drug exemption (IND), or a Tracked Safety Issue (TSI)—so this review is unusual in pertaining to numerous drugs spanning several pharmacological classes.
3. Most reviews involve a collaborative effort among staff members with specialized expertise relevant to the material at hand. As needed, this specialized expertise might include a pharmacologist or toxicologist to review carcinogenicity, a medical

[1] *Never approved.*

officer (like Dr. Marciniak) to review clinical findings, and a statistician or pharmacometrician to explore relationships between exposure to a drug and clinical events. This review was unusual in its lack of involvement or collaboration with other staff with potentially critical expertise.

4. Reviews of this magnitude almost always involve discussions with more senior managers, intended to enrich the perspectives on the work through constructive feedback and dialog. This review was unusual in that no one senior to Dr. Marciniak in either the Division or ODE-I was given the opportunity to discuss the review with Dr. Marciniak in advance of, or subsequent to, its being finalized and filed. We wish to emphasize that, in bypassing management in this manner, Dr. Marciniak was not avoiding censure or being ordered to desist. As Dr. Marciniak knew well, he had the right to present his own perspectives on the matter at hand, and, if he were unhappy with management's opinions or handling of his concerns, he knew he had the opportunity to appeal the Division's decision to ODEI, ODEI's decision to OND, and OND's decision to the CDER Center Director. We note, too, that scientific disagreements within the Office of New Drugs are not unexpected, and the normal review and appeal process ensures that each professional viewpoint has been fully developed, understood, and considered.
5. Because the new drug applications to which he filed his review were not assigned to him, his review was unexpected, and in many cases filed without knowledge of the team actually assigned to review the new drug.
6. Important endpoints in clinical trials are often adjudicated, typically by a committee of experts who make judgments based on standard criteria defined in a manual. For example, judgments on whether a patient had a heart attack, stroke, or a hospitalization for a particular medical condition, are often adjudicated by a committee of experts. CDER policy[2] is that reviewers should survey the adjudication process to form an opinion as to the reliability of the process and the conclusions reached. Reviewers are strongly discouraged, however, from undertaking the wholesale readjudication of data as Dr. Marciniak did here, but particularly in an unblinded fashion. When problems are uncovered, the matter is expected to be referred back to the applicant to have blinded readjudication performed by experts, based on pre-defined criteria.

   Much of Dr. Marciniak's review is based on his view as to whether particular adverse events reported in clinical trials constituted evidence of cancer progression. Dr. Marciniak made such decisions by himself, with full knowledge of treatment assignment (i.e., without blinding). We have not been able to verify the particular counts of cancer events that Dr. Marciniak reported.

What then is Dr. Marciniak's thesis? The review consists of 347 pages as follows:

Pages 1-63	Body of the review
Pages 64-250	Slides produced by HCRI with preliminary analyses of the DAPT study, dated 22 August, 5 September, 17 September, and 24 October 2014
Pages 251-290	A review filed to TSI 935 by Dr. Marciniak of ARBs and cancer, dated 7 March 2013
Pages 291-346	Dr. Marciniak's analysis plan for ARBs and cancer, dated 18 August

[2] *MaPP 6010.3, published in 2010 and available at http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM229716.pdf.*

	2012.
Page 347	Electronic signature

Dr. Marciniak summarizes his concerns in the paragraph preceding his recommendations:[3]

> *"I conclude that the totality of evidence strongly supports that prolonged thienopyridine use is associated with increased rates of solid cancers, at least in patients undergoing invasive procedures. The evidence also suggests that the association is not limited to inhibition of the $P2Y_{12}$ receptor but extends to the PAR-1 receptor. The totality of evidence also supports that excess bleeding from higher anticoagulant dosing also increases the risk of solid cancers. Hence the increased solid cancer risk appears to be related to inhibition of coagulation and not inhibition of a particular receptor or use of a particular drug, i.e., it is a "class" effect. I provide recommendations below based on these conclusions as well as my observations regarding trial conduct problems in the 23 trials analyzed."*

As background, we note that Dr. Marciniak's reviews focus mainly on two distinct types of drugs: anti-platelet drugs and anti-coagulants. Thienopyridines (clopidogrel, prasugrel) are anti-platelet drugs of a particular structural class; they block the $P2Y_{12}$ receptor in platelets. In so doing, they have benefit in preventing blood clots leading to heart attacks, but they also exacerbate bleeding. Vorapaxar is a different type of anti-platelet drug that blocks the PAR-1 platelet receptor. Although voraxapar differs in structure from the thienopyridines and blocks a different platelet receptor, it has a similar indication and similar effects on bleeding.

Anticoagulants are entirely distinct from anti-platelet drugs, both structurally and functionally. They interfere with the non-cell-based blood coagulation process. They fall into several structural classes, and, among other things, are approved to prevent strokes in patients with non-valvular atrial fibrillation. Despite the marked differences between anti-platelet drugs and anti-coagulants, they share the propensity to worsen bleeding.

In brief, his thesis is that drugs that worsen bleeding somehow worsen the risk of cancer—not a specific type of cancer or a related group of cancers, but all types.

In addition, Dr. Marciniak holds the belief that angiotensin receptor blockers (ARBs), a completely unrelated class of drugs, increase the risk of cancer.

Here we will address most of the issues Dr. Marciniak raises with regard to the potential for antiplatelet drugs, anticoagulants, and ARBs to increase the risk of cancer.

In the quoted paragraph, Dr. Marciniak refers to "23 trials analyzed." The body of the memo discusses his findings from the following studies:

Study	**Comparison**
ACTIVE-A	Clopidogrel vs. aspirin
ACTIVE-W	Clopidogrel vs. warfarin
APPRAISE	Apixaban vs. warfarin

[3] *Page 8.*

ARISTOTLE	Apixaban vs. warfarin
ATLAS	Rivaroxaban vs. placebo
AVERROES	Apixaban vs. aspirin
CAPRIE	Clopidogrel vs. aspirin
CHARISMA	Clopidogrel vs. placebo
CREDO	Clopidogrel vs. placebo
CURE	Clopidogrel vs. placebo
DAPT	Clopidogrel or prasugrel vs. placebo
ENGAGE	Edoxaban vs. warfarin
J-ROCKET	Rivaroxaban vs. warfarin
PLATO	Ticagrelor vs. clopidogrel
PRoFeSS	Clopidogrel vs. aspirin
RE-LY	Dabigatran vs. warfarin
ROCKET	Rivaroxaban vs. warfarin
SPORTIF III	Ximelagatran vs. warfarin
SPORTIF V	Ximelagatran vs. warfarin
SPS3	Clopidogrel vs. placebo
TRA2P	Vorapaxar vs. placebo
TRACER	Vorapaxar vs. placebo
TRILOGY	Prasugrel vs. clopidogrel
TRITON	Prasugrel vs. clopidogrel

The Marciniak review was filed shortly before the Division Director memo (22 December 2014) and Office memo (8 January 2015) documenting the action for edoxaban. His review was not expected and went unnoticed by the review team. Thus, his review was not discussed in our memos documenting our regulatory decision on that application. Before discussing Dr. Marciniak's general concern about cancer in patients treated with anti-platelet and anticoagulant drugs, we briefly address edoxaban, which is mentioned in the first summary paragraph of Dr. Marciniak's review:

> *The most recent submission for a new anticoagulant, edoxaban, is typical in providing, by itself, suggestive but not conclusive evidence for the association [with cancer].*[4]

The "suggestive" data are further described in Table 15[5] (reproduced below), which gives Dr. Marciniak's estimated relative risk estimate from his counts of cancers in ENGAGE, a study that compared edoxaban (two dose levels) and warfarin. The data show [6] (RR) =

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[4] *Page 1.*

[5] *Page 37.*

[6] *"Relative risk", i.e., how many times more likely some experimental intervention is to cause an event (in this case, cancer) than is some control.*

1.0 with 95% confidence interval (CI) of 0.9-1.1; i.e., there is no evidence of any overall effect on cancer in ENGAGE, at least compared with warfarin.

Warfarin is an anticoagulant that causes at least as much bleeding as edoxaban does, so that there is no plausible reason, given Dr. Marciniak's hypothesized relationship, to expect a higher rate of cancer with edoxaban; indeed, the rate should be lower. As Table 15[7] clearly shows, solid cancer rates were not increased compared with warfarin for any of the newer anticoagulants.

Table 15: New Oral Anticoagulant Outcome Trials 2

New oral anticoagulant	rivaroxaban	dabigatran	edoxaban	ximelagatran	
Trial	J-ROCKET	RELY	ENGAGE	SPORTIF III	SPORTIF V
Dates randomized	06/07-11/08	12/05-12/07	11/08-11/10	08/00-09/01	08/00-12/01
Population	afib	afib	afib	afib	afib
N	1,280	18,113	21,105	3,407	3,922
Age, median y	72	72	72	71	73
Male	80%	64%	62%	69%	69%
Invasive	NA	NA	NA	NA	NA
Control	warfarin	warfarin	warfarin	warfarin	warfarin
Clopidogrel use	NA	6%	2.3%	0%	o%
Aspirin use	38%	40%	30%	12%	18%
Follow-up, median m	19	24	34	15	20
New drug discontinuation	26%	24%	34%	18%	37%
Complete follow-up	90%	91%	90%	88%	83%
Died	1.8%	7.6%	10.8%	4.4%	6.1%
Major/severe bleed RR	0.9	0.9	0.7	0.7	0.7
95% CI	0.5-1.4	0.8-1.0	0.6-0.8	0.5-1.1	0.5-1.0
Solid cancer RR	0.9	1.1	1.0	1.0	0.8
95% CI	0.5-1.7	0.9-1.3	0.9-1.1	0.7-1.5	0.6-1.1
Solid ca/100 PEY (control)	1.9	2.1	1.7	1.8	2.7
Non-CV death RR	0.3	1.0	1.0	0.7	0.7
95% CI	0.1-1.4	0.8-1.2	0.9-1.2	0.4-1.3	0.5-1.1
Died with solid ca RR	1.0	0.9	1.1	1.3	0.7
95% CI	0.1-16	0.7-1.2	0.9-1.4	0.6-3.2	0.4-1.3
Died %, solid ca pts (control)	5%	32%	30%	21%	30%

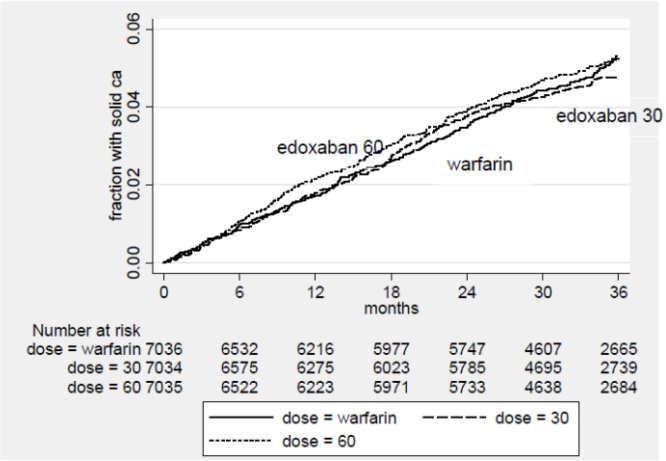
PEY = person exposure year; RR = risk ratio new drug/control; CI = confidence interval

Despite there being no overall effect, Dr. Marciniak goes on to analyze the two doses of edoxaban in ENGAGE separately in Figure 28[8] (reproduced below), which again shows no evidence of a difference.

[7] *Page 37.*

[8] *Page 53.*

Figure 28: Solid Cancer Event Incidence in ENGAGE



Having found no effect for pooled doses and no effect by dose, Dr. Marciniak finds four specific cancer types (colon, esophageal, lung, and pancreas) whose analyses by dose "appear to be informative."[9] He does not list all cancers and does not give p-values for any of the 8 comparisons (two doses and four cancer types) he finds "informative." He also tells us nothing about other cancer types, so you cannot tell whether these trends are likely to be chance. Nor does he mention other cancers for which there were trends for lower rates on edoxaban (which there surely were, given the overall RR of 1.0).

Dr. Marciniak does not mention the detailed clinical review[10] of record for edoxaban by Drs. Blank and McDowell. This review was considered in the approval of Savaysa, and it was available to Dr. Marciniak, too. Drs. Blank and McDowell looked specifically at malignancy in the edoxaban development program, both as adverse events specific to cancer types as reported by the investigator and through broader groupings called Standardized MedDRA Queries. For the most part, the reviewers saw the absence of risk overall as reassuring, but they did tabulate cancers by type, and we show the complete list of cancer event rates from that review[11] below:

[9] *Page 53.*

[10] *Dated 10 October 2014*

[11] *Page 210 of NDA Clinical Review by Drs. Blank and McDowell, dated 10 October 2014*

Table 96 Investigator Reported Clinically Evident Post Randomization Malignancies by Location, overall study period

Malignancies Category/Location	Edoxaban 30mg (15mg DosAdj) (N=7002)		Edoxaban 60mg (30mg DosAdj) (N=7012)		Warfarin (N=7012)	
	n	Event Rate (%/yr)	n	Event Rate (%/yr)	n	Event Rate (%/yr)
Any Location	463	2.50	494	2.68	485	2.64
Skin[a]	150	0.80	178	0.95	163	0.87
Small or Large Bowel	51	0.27	52	0.27	60	0.32
Lung	44	0.23	50	0.26	40	0.21
Prostate	48	0.41	48	0.41	53	0.45
Bladder	29	0.15	32	0.17	29	0.15
Breast	21	0.11	25	0.13	27	0.14
Stomach	15	0.08	19	0.10	20	0.11
Other	23	0.12	17	0.09	17	0.09
Pancreatic	16	0.08	16	0.08	10	0.05
Esophageal	13	0.07	14	0.07	4	0.02
Multiple	3	0.02	13	0.07	11	0.06
Liver, Gall Bladder, or Bile Ducts	18	0.09	10	0.05	17	0.09
Lymphoma	6	0.03	10	0.05	8	0.04
Lip, Oral, Pharynx	15	0.08	9	0.05	9	0.05
Uterine	7	0.09	8	0.11	6	0.08
Leukemia	12	0.06	6	0.03	13	0.07
Renal	8	0.04	6	0.03	12	0.06
Thyroid	1	0.01	6	0.03	2	0.01
Brain	6	0.03	5	0.03	8	0.04
Genital	3	0.02	3	0.02	8	0.04
Other Respiratory (Excluding Lung)	1	0.01	2	0.01	1	0.01
Unspecified	8	0.04	2	0.01	4	0.02

Source: CSR Table 12.25

We see confirmation that the overall event rates are similar on warfarin and edoxaban, at about 2.6%/year. Of the cancer types Dr. Marciniak highlighted, we see similar rates on warfarin and edoxaban for small and large bowel cancer (0.3%/year), lung (0.2%/year), pancreas (<0.1%/year), and esophagus (<0.1%/year). While some of these cancers trend higher on edoxaban than warfarin, both doses of edoxaban look better than warfarin for prostate, breast, stomach, leukemia, renal, brain, and genital cancers. Dr. Marciniak not remark upon these trends that appear to favor edoxaban and run contrary to his thesis. In our view, these data are all consistent with there being no overall effect of edoxaban on cancer. With no difference overall between edoxaban and warfarin, in order to believe that edoxaban causes certain cancers (compared to warfarin), one would have to believe that edoxaban prevents other cancers, or that edoxaban causes some cancers and warfarin causes others. Clearly, this is not plausible or rational.

Moreover, as noted, if one's theory was that cancer risk related to bleeding, then it is not clear to us why one would expect there to be any increased risk of a novel anticoagulant compared with warfarin, because warfarin and these other anticoagulants cause similar rates of bleeding.

We conclude there is no evidence for an increased risk of cancer with edoxaban. Dr. Marciniak's basis for finding the evidence "suggestive" is not apparent to us.

Dr. Marciniak's recommendations

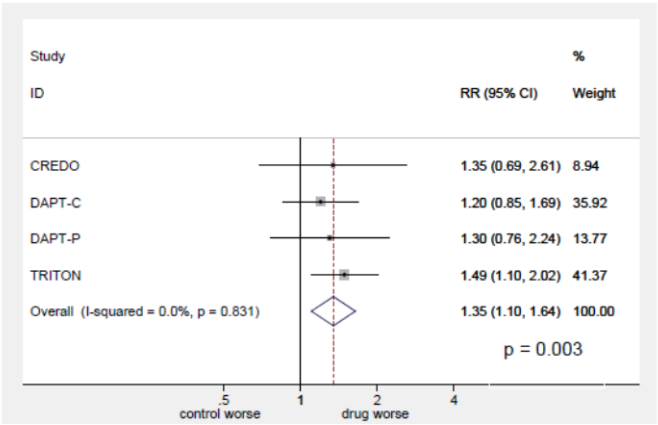
Dr. Marciniak makes a series of specific recommendations[12] reflecting his conclusions about drugs that increase the risk of bleeding and cancer, and we address below the arguments he poses in support of those recommendations:

1. *"The FDA should provide practitioners and patients with the data regarding the association between bleeding and solid cancers as soon as possible."* He goes on (his item 2) to suggest methods of communication, including a safety communication, posting his review, and holding an Advisory Committee meeting covering this topic and ARBs and cancer (see below). All of his recommendations depend on a conclusion that the data do indeed suggest that the bleeding/cancer relationship is credible. We address "bleeding and solid cancers" first, and then discuss "ARBs and cancer."

   Although one might reasonably address such a hypothesis by looking at all relevant studies of antiplatelet and anticoagulant drugs together, Dr. Marciniak does not do that. He first discussed the antiplatelet drugs, so we do too.

   With regard to thienopyridines and cancer, Dr. Marciniak provides this meta-analysis:[13]

Figure 1: Meta-Analysis of Solid Cancer Events in the Thienopyridine Trials with Substantial Invasive Approach and for Which the FDA Has Cancer Data



   Although there are many other thienopyridine studies, Dr. Marciniak opted to show pooled data representing only four comparisons from three studies: clopidogrel vs. placebo in CREDO, 12- vs 30-month treatment in the clopidogrel subset of DAPT, 12- vs. 30-month treatment in the prasugrel subset of DAPT, and clopidogrel vs. prasugrel in TRITON. Note that in TRITON, we are comparing two drugs with quite similar rates of bleeding, so, if the bleeding were predictive of cancer, the rates of cancer should be most similar for this study.

   His decision to limit his meta-analysis to studies for which data were available might have been reasonable and unbiased, but he stated that he restricted his analysis to studies "with substantive invasive approach." Such a restriction is odd, and does not seem relevant to his hypothesis. Here is how he explains it:[14]

   > *"The results of the antiplatelet drug trials without a substantial invasive approach contrast with those shown in Figure 2. The older*

[12] *Pages 8-10.*

[13] *Page 2.*

[14] *Page 5*

> *non-invasive clopidogrel trial results do not support a relationship between clopidogrel use or bleeding and solid cancers. All trials had study limitations that I discuss in the Clopidogrel and Cancer section that limit their validity. Prasugrel TRILOGY in medically managed ACS is similarly negative, although TRILOGY, like PLATO, had serious conduct problems. Vorapaxar TRA2P, a very large trial in high risk patients, was neutral for solid cancers and non-CV deaths despite substantially higher bleeding in the vorapaxar arm. However, TRA2P had a design flaw similar to the ones in the two large clopidogrel studies (CAPRIE and CHARISMA) that also produced neutral results: CAPRIE did not count adverse events (AEs) more than 28 days after study drug discontinuation; CHARISMA defined AEs as occurring within 28 days of treatment discontinuation; and TRA2P did not solicit AEs that occurred more than 60 days after the last dose."*

We note that the Figure 2[15] to which Dr. Marciniak refers shows nothing relevant to this question, nor does any other figure in this review. Instead we see a series of excuses for excluding studies for a variety of reasons—perceived "study limitations," design, conduct, or analysis issues—none of which have anything to do with an "invasive approach" and none of which bias against finding an effect of treatment on cancer. All share the common feature of failing to support his hypothesis—the purported association with cancer. We note that, with the nominal results at his disposal, Dr. Marciniak knew the implications of his decisions to include or exclude various studies on the results of his meta-analyses. We describe below the cancer findings for the 5 studies mentioned above that Dr. Marciniak specifically discounts as not being credible—TRILOGY, PLATO, TRA2P, CAPRIE, and CHARISMA.

TRITON vs. TRILOGY

Three of the comparisons incorporated in Figure 1 are against placebo, but TRITON compared prasugrel with clopidogrel. Because prasugrel and clopidogrel caused similar rates of bleeding, one might have expected similar rates of bleeding-related cancer. However, of the studies Dr. Marciniak utilized for the analysis in Figure 1, TRITON shows the greatest relative risk, with prasugrel worse than clopidogrel. The Division's assessment of TRITON is in the Deputy Division Director's memo.[16] There was no signal in non-clinical carcinogenicity assessments for prasugrel, and the Division and ODE-I concluded the signal was likely chance or driven by bleeding that led to cancer discovery. The approved labeling says:

> *"During TRITON-TIMI 38, newly diagnosed malignancies were reported in 1.6% and 1.2% of patients treated with prasugrel and clopidogrel, respectively. The sites contributing to the differences were primarily colon and lung. It is unclear if these observations are causally-related or are random occurrences."*

A subsequent study—TRILOGY—was getting underway as prasugrel was approved, and, to follow up on TRITON, the sponsor was asked to assess cancer as an event of special interest in that study. Dr. Marciniak's analyses of TRILOGY revealed no increased risk of cancer with prasugrel, but he reiterated his concerns about the interpretation of cancer data in TRILOGY,[17] although he failed to name concerns

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[15] *Page 3. The figure is entitled "Meta-Analysis of Solid Cancer Events in the Antiplatelet and Anticoagulant Trials with Substantial Invasive Approach and Having a Major Bleed RR ≥ 1.2 and for Which the FDA Has Cancer Data", and we show it below.*

[16] *NDA 22307, CDTL review dated 9 January 2009.*

[17] *Page 24-26.*

that would lead to bias. He described small sample size, loss to follow-up, and low cancer incidence rates as problems, but we note that these factors do not lead to bias.

In fact, TRILOGY compared prasugrel and clopidogrel in 9326 subjects over 14 months. It was carefully designed to assess new cancers, in part to fulfill the post-marketing requirement by FDA. The results from a total of 11718 patient-years of exposure were about 14 new cancers per 1000 patient-years, the same on prasugrel and clopidogrel. Dr. Marciniak's review counts fewer cancer events, but found fewer events on prasugrel than on clopidogrel, the opposite of the finding in the earlier TRITON study. The Division's conclusions[18] from TRILOGY were that the data were reassuring and no less likely to be correct than were the findings of TRITON.

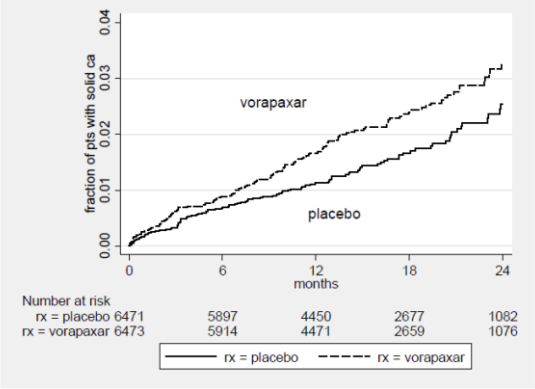
PLATO

PLATO compared ticagrelor and clopidogrel in 18624 subjects over a median of 10.5 months. By Dr. Marciniak's counts, there were 15 cancers per 1000 patient-years on clopidogrel and about 13 per 1000 patient-years on ticagrelor—about the same rates reported in TRILOGY. Dr. Marciniak discounts this reassuring finding[19] because of its "short duration and incompleteness of follow-up," neither of which introduces bias.

TRACER vs. TRA2P

TRACER compared vorapaxar with placebo in 12944 subjects followed for a median of about 15 months. Dr. Marciniak's counts of events in this study are reproduced below:

Figure 10: Solid Cancer Event Incidence in TRACER



TRACER was stopped early for futility, so it has *lots* of missing data, yet here Dr. Marciniak did not consider the missing data to be a deficiency. He did note that the curves diverge before any new cancer could grow large enough to be discovered, which he attributes to "detection bias," bleeding that leads to earlier discover of pre-existing cancer. We agree. A much larger study of vorapaxar, TRA2P, strongly suggests that the TRACER finding is a chance occurrence and not a drug effect at all. TRA2P compared vorapaxar with placebo in 26449 subjects followed for a median of about 2.5 years. Twice as large and twice as long as TRACER, TRA2P included ~4 times as many patient-years of experience. According to Dr. Rose's clinical review,[20] there were about 14.8 cancer events per 1000 patient-years on

[18] *NDA 22307 Division Director memo dated 15 October 2013.*

[19] *Page 32.*

[20] *Page 123 of a review dated 16 December 2013 and co-signed by Dr. Marciniak as team leader.*

placebo and 14.4 per 1000 patient-years on vorapaxar. Dr. Marciniak dismisses TRA2P in a paragraph[21] without saying more than it is discrepant with TRACER. Why? "*Its one identified design flaw is that the protocol specified phone contacts for patients who had discontinued treatment....*" We understand how incompleteness of follow-up might have led to missing events, but not how such missingness could have biased one group over another in TRA2P. We also cannot understand why missingness rendered TRA2P uninterpretable but did not impede TRACER's interpretation, given that the extent of missing data was greater in TRACER.

All in all, we conclude that the placebo-controlled data on vorapaxar do not suggest any increase in cancer risk; Dr. Marciniak's omission of TRA2P was not scientifically justifiable. In this placebo-controlled trial where there was unequivocally more bleeding in the voraxapar group than the placebo group, Dr. Marciniak rejected use of the data, presumably because they rebutted his assertion that bleeding causes cancer.

CAPRIE

CAPRIE compared clopidogrel and aspirin in 19185 subjects followed for 23 months. By Dr. Marciniak's counts, there were 14 cancers per 1000 patient-years on aspirin and 14 per 1000 patient-years on clopidogrel. Dr. Marciniak discounted CAPRIE because its analysis only included events identified within 28 days of study drug discontinuation; whether optimal for capturing cancer events or not, this rule was applied to both treatment groups. This is certainly not biased to hide events on clopidogrel, and, once again, Dr. Marciniak rejected data that rebutted his assertion that bleeding causes cancer.

CHARISMA

CHARISMA compared clopidogrel and placebo in 15603 subjects followed for 28 months. By Dr. Marciniak's counts, there were 10 cancers per 1000 patient-years on placebo and 9 per 1000 patient-years on clopidogrel. Dr. Marciniak discounts CHARISMA for the same reason as he does CAPRIE.

In each of these cases—TRILOGY, PLATO, TRA2P, CAPRIE, and CHARISMA—the studies were as large or larger than the studies Dr. Marciniak included in his meta-analysis. In three cases, the findings are inconsistent with studies of the same drug that Dr. Marcinak included, and all five of these studies show no evidence for a cancer signal. Three of these studies—TRA2P, CAPRIE, and CHARISMA—compared a drug with placebo or aspirin, settings where the any cancer-promoting potential should have been clearer than in comparisons with another antiplatelet medication. We conclude that there was no reasonable basis for excluding the studies that failed to sustain Dr. Marciniak's hypothesis.

DAPT

Dr. Marciniak did include two subgroup analyses of DAPT. DAPT was a randomized comparison of 12 months and 30 months on aspirin plus thienopyridine (clopidogrel or prasugrel at the investigator's discretion) following placement of a drug-eluting or bare-metal coronary artery stent. Dr. Marciniak's description of this study's results[22] was based upon *"preliminary results to the FDA in four PowerPoint presentations"* and one publication. The Agency's assessment of DAPT is available in a Drug Safety Communication,[23] but it is unclear how these results met Dr.

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[21] *Page 32.*

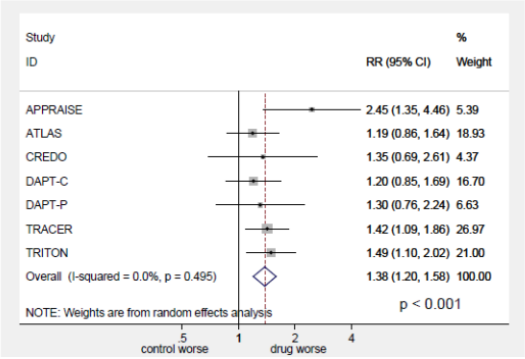
[22] *Pages 10-17.*

[23] *http://www.fda.gov/drugs/drugsafety/ucm471286.htm*

Marciniak's inclusion criteria for studies for his meta-analysis. He stated that he included studies *"for which the FDA has cancer data,"* but he did not have access to the DAPT data.

After presenting his analysis of antiplatelet drugs alone, Dr. Marciniak presented his more integrated analysis of antiplatelet and anticoagulant drugs and risk of cancer, shown in Figure 2:[24]

Figure 2: Meta-Analysis of Solid Cancer Events in the Antiplatelet and Anticoagulant Trials with Substantial Invasive Approach and Having a Major Bleed RR ≥ 1.2 and for Which the FDA Has Cancer Data



Of various candidates, he included selected placebo-controlled studies in acute coronary syndrome (ACS)—APPRAISE (apixaban; 7392 subjects followed for 8 months), ATLAS (rivaroxaban, 15526 subjects followed for 14 months), and TRACER. But note that we are now looking at a further subgrouping—not just *"trials with a substantial invasive approach"* and *"for which the FDA has cancer data,"* but also trials *"having a major bleed RR ≥ 1.2."* This additional selection criterion has some plausibility as a factor in bringing to light latent cancers, especially GI cancers, but that does not lead to any ominous conclusions regarding the suspect drugs.

Dr. Marciniak acknowledges the possibility that early separations in event rates for particular cancers (whether or not nominally significant) may represent bleeding leading to discovery;[25] he thinks that cases where the separation appears late (whether or not nominally significant) represent true promotion.[26] Tabulated,[27] but not included in the presented meta-analysis are results for ARISTOTLE (apixaban vs. warfarin, n=18201, RR for cancer of 0.9), AVERROES (apixaban vs. aspirin, n=5598, RR for cancer of 1.1), ROCKET (rivaroxaban vs. warfarin, n=14264, RR for cancer of 1.1), J-ROCKET (rivaroxaban vs. warfarin, n=1280, RR for cancer of 0.9), RELY (dabigatran vs. warfarin, n=18113), ENGAGE (edoxaban vs. warfarin, n=21105, RR for cancer of 1.0), SPORTIF III (ximelagatran vs. warfarin, n=3407, RR for cancer of 1.3) and SPORTIF V (ximelagatran vs. warfarin, n=3992, RR for cancer of 0.7).

What was wrong with them? According to Dr. Marciniak's review, ARISTOTLE,[28] AVERROES,[29] and ROCKET[30] failed the test for 20% worse bleeding. (That did not

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[24] *Page 3.*

[25] *E.g., comment on page 41.*

[26] *E.g., comment on page 44.*

[27] *Pages 36 and 37.*

[28] *Page 41.*

[29] *Page 44.*

prevent Dr. Marciniak from pointing out a few adverse trends among cancer types.) ATLAS[31] had problems with follow-up, but that did not prevent inclusion in the meta-analysis nor did it prevent description of selected adverse cancer findings. No reason is given for excluding J-ROCKET.[32] RELY[33] had 20% lower bleeding on the 110-mg dose than on warfarin, but no difference from warfarin on cancers that Dr. Marciniak counts;[34] it gets discounted *"because dabigatran [110 mg only?] caused a different pattern of bleeding than [did] warfarin."* He excluded ENGAGE because it had incomplete follow-up (but 34 months of it), markedly less bleeding on edoxaban than on warfarin, and no difference he could identify in cancers. Likewise, SPORTIF III and V both showed less bleeding on ximelagatran than on warfarin with no difference in cancers identified by Dr. Marciniak.

Also unmentioned are numerous trials of reasonable size and duration supporting the use of anticoagulant drugs in settings of deep venous thrombosis and shorter-term studies of these drugs for a period following joint surgery.

Finally, none of these drugs has any non-clinical signal for new cancers or for tumor promotion in animal life-time carcinogenicity studies.[35]

ARBs and cancer

With regard to ARBs and cancer, Dr. Marciniak asserts[36] that FDA *"suppressed the evidence associating ARBs with lung cancer: Almost five years after the association of ARB use with cancer was first published (Sipahi, Debanne et al. 2010), the FDA still has not released the evidence that the risk of lung cancer with ARB use is real."* Dr. Marciniak's accusation is completely without merit. This matter was reviewed in TSI #935. The findings of thus safety review were announced to the public in a Drug Safety Communication[37] on 2 June 2011. We concluded that there was nothing to "suppress," and we are puzzled by Dr. Marciniak's ignorance of this response.

2. *"The FDA should review all of the data regarding duration of dual antiplatelet therapy post-stenting and integrate it with these data regarding bleeding and cancer. Based on this review the FDA should recommend changes to the labels of antiplatelet drugs to include warnings regarding solid cancers and recommendations for duration of antiplatelet therapy and for investigating possible cancer signals. The FDA should also recommend changes to the labels of anticoagulants noting the data regarding anticoagulants and cancer and including recommendations for investigating possible cancer signals."*

   Despite many discussions with each of us and others at FDA during his tenure at FDA, Dr. Marciniak has failed to produce plausible evidence of a risk for any of the named drug classes or specific members thereof. His choices of which studies to include and which analyses to do or show appear to select studies for analysis and presentation that support the signal he expects to see. He denigrates or ignores

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[30] *Page 47.*

[31] *Page 44.*

[32] *Page 47.*

[33] *Page 48.*

[34] *Pages 48-49, Table 19.*

[35] *Apixaban NDA 202155, Pharmacology/toxicology review dated 21 February 2012, page 70ff; rivaroxaban NDA 202439, pharmacology/toxicology review dated 1 August 2011, page 60ff; vorapaxar NDA 204866, pharmacology/toxicology review dated 17 December 2013, page 124ff.*

[36] *Page 8.*

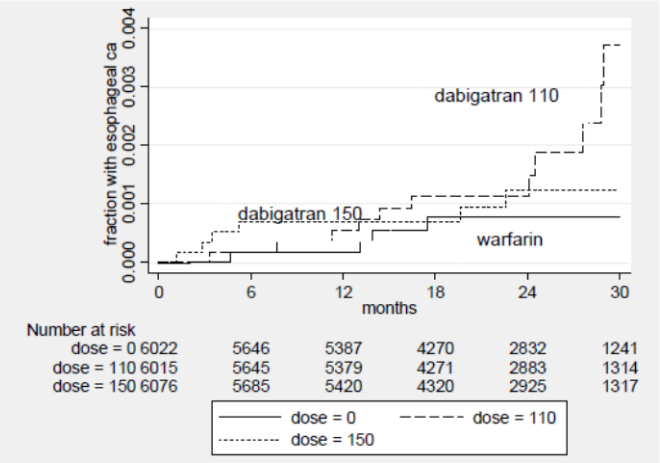
[37] http://www.fda.gov/Drugs/DrugSafety/ucm257516.htm

good quality studies whose findings do not support his thesis, finding them all flawed without really providing support for those conclusions. We reject as without support the hypothesis that bleeding or drugs that cause bleeding cause cancer or lead to cancer promotion. We therefore do not believe that we have cause for amending labels for antiplatelet drugs, anticoagulants, or ARBs. While FDA will, of course, continue to monitor emerging safety signals in new studies with these drugs and in the post-marketing setting, we lack any case for directing more active surveillance.

3. *"The FDA should inform the sponsors about the signal for esophagus cancers with NOACs, request their proposals for elucidating it, and design or commission drug surveillance database studies to address the signal."*

   Dr. Marciniak finds the following data supportive of an association between dabigatran and esophageal cancer:[38]

Figure 25: Esophagus Cancer Event Incidence in RELY



These results are described as follows:[39]

> *"The breast and esophagus cancer incidence curve suggest similar, higher rates than warfarin for both doses. Whether these are real differences or chance variation cannot be distinguished definitively from this size study. The esophagus cancer increase late appears relevant because one established dabigatran adverse effect is GI irritation. If this increase in esophagus cancer is real the late disparity between the doses would likely be the result of chance."*

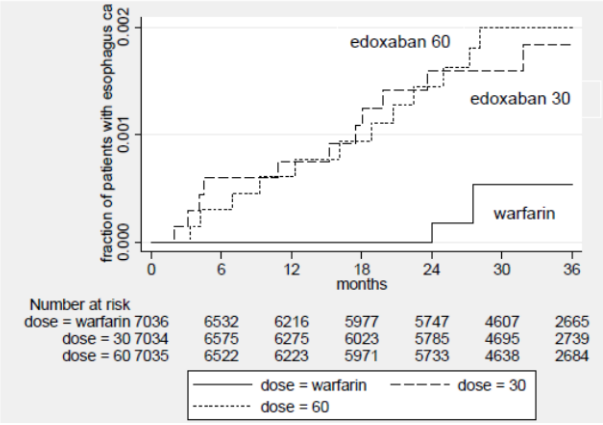
Although he selectively provided a nominal p-value for some other associations he described, he did not provide a p-value for this. We suspect this finding was not close to being statistically significant, even before considering multiplicity adjustment for 25 categories of solid cancer types he described in the RELY database. He concluded that the disparity of the effect of the two doses is likely the result of chance. We would conclude that the inconsistency in the findings between the lower and higher doses of dabigatran strongly suggests that the 'finding' with the lower dose is due to chance. With the higher dose of dabigatran, the dose that is marketed in the U.S., there is no finding whatsoever.

[38] *Page 51.*

[39] *Page 52.*

Here are the data Dr. Marciniak found suggestive of risk of esophageal cancer on edoxaban from the ENGAGE study:[40]

Figure 30: Esophagus Cancer Event Incidence in ENGAGE



Dr. Marciniak's description of this result was as follows:

> *"Esophagus cancer incidence was much higher and similar in both edoxaban arms. The incidence curves start diverging early from warfarin's. While one would be tempted to dismiss the differentiation as chance, the fact that both edoxaban arms are similar and the differentiation of esophagus cancer with dabigatran (although with a difference time course), suggests that we shouldn't dismiss this finding."*

This apparent association looks more plausible than the association with dabigatran, but again no p-value is provided, and we cannot even guess at the magnitude of multiplicity problem here, because of the myriad of types of solid tumors analyzed. This is one of four cancer types subjected to time-to-event analyses from ENGAGE, but we cannot determine how many others were performed. In addition, warfarin causes at least as much bleeding as edoxaban does or the other non-vitamin K-dependent oral anticoagulants (NOACs) do, so these data hardly support an effect of bleeding per se.

Dr. Marciniak found an association between ximelagatran and esophageal cancer: 3 cases vs 0 on warfarin in the SPORTIF III study and 2 vs 0 in SPORTIF V. Again, it is difficult to assess the multiplicity problem, but he does, for SPORTIF V, tabulate[41] more cancers on warfarin overall, with trends for breast (11 on warfarin vs. 2 on ximelagatran) and melanoma (8 on warfarin vs 4 on ximelagatran). Although these are more impressive than any adverse trends with ximelagatran, they go without much comment by Dr. Marciniak.[42]

The associations of esophageal cancer with edoxaban, dabigatran, and ximelagatran are all weak. What about the associations with other NOACs? By Dr. Marciniak's counts, there was one case in each of the two rivaroxaban arms in ATLAS, one on apixaban in APPRAISE, and 3 on apixaban vs 2 on warfarin in ARISTOTLE. Thus, these do not show much of a signal, either. We cannot determine why Dr. Marciniak excluded data from other large studies of these drugs.

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[40] *Page 54.*

[41] *Pages 58-59.*

[42] *Page 61.*

Although we do not believe there is any evidence that NOACs, individually or as a class, cause esophageal cancer, we would not have been surprised to see some association resulting from cancer discovery precipitated by esophageal bleeding events. In fact there is scant evidence for NOACs in general to predispose to esophageal cancer:[43]

NOAC	Study	RR for hemorrhage	Esophageal cancer cases	
			Control	NOAC
Apixaban	ARISTOTLE	0.6	2	3
Edoxaban	ENGAGE	0.7	N/A	N/A
Ximelagatran	SPORTIF III	0.7	0	3
Ximelagatran	SPORTIF V	0.7	0	2
Rivaroxaban	J-ROCKET	0.9	N/A	N/A
Dabigatran	RELY	0.9	3	8
Rivaroxaban	ROCKET	1.0	N/A	N/A
Apixaban	AVERROES	1.1	N/A	N/A
Rivaroxaban	ATLAS	2.3	0	1
Apixaban	APPRAISE	2.6	0	1

We conclude that there is an inadequate basis for any of Dr. Marciniak's recommendations with regard to NOACs and an association with esophageal cancer.

4. *"Vital status ascertainment in trials should be > 99% of all randomized subjects. All trials should capture the identifiers needed for national death registry indexing. If regions refuse to allow passive follow-up of vital status for trial subjects, e.g., registry access, then the trial sponsor should not conduct trials for U.S. registration in those regions."*

   The impact of missing data, particularly for mortality, is universally appreciated, and we believe that we generally get good ascertainment. As Dr. Marciniak surely knew, at least for major outcome studies with some expectation of mortality, the Division has long been routinely recommending studies be conducted in regions where follow-up for vital status is possible through passive means.

5. He recommends that studies generally should assess events of particular interest (death, cancer, MIs, stroke, and major thrombotic events) at the end of study, preferably at a final visit. He also suggests that "…[case report forms] for visits should be recorded and submitted in real time…."

   We believe that we get reasonable assessment of adverse events of special interest. In addition, we believe there is little potential for bias from cases missed because of loss to follow-up (which is not generally related to cancer) or incomplete ascertainment of events.

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[43] *RR for major/severe bleeding come from Dr. Marciniak's Tables 14 and 15 (pages 36-37). Where available, counts of events come from his review, too. Studies with two doses of a NOAC are the mean of the two doses. Dr. Marciniak's review does not have counts of esophageal cancer events for ENGAGE (edoxaban), and they are not in the primary clinical review of ENGAGE.*

We regard the request for real-time submission of case report forms (CRFs) to be unreasonable. First, the sponsor invests considerable effort in the quality control of data we receive. We share Dr. Marciniak's interest in understanding the effect of quality assurance processes, but we as an agency are ill-equipped to review CRFs in real time. Moreover, companies typically find errors in CRFs, and query investigators with respect to missing data, incomplete data, data that appear erroneous, etc. In other words, CRFs are subjected to auditing and quality control prior to submission to FDA (the audit trail is available to FDA, if needed).

6. He recommends good quality data collection regarding cancer events. We agree and think that generally we get good quality reporting and response to requests for additional follow-up.

We began by outlining some unusual and inefficient aspects of Dr. Marciniak's work on this problem. Most troubling among these was the failure to involve colleagues and supervisors. Dr. Marciniak did not involve pharmacologists or toxicologists, who have uniformly concluded there is a lack of non-clinical evidence for carcinogenic potential for any of these drugs. He did not consult statisticians who might have alerted him regarding the hazards of cherry-picking studies to pool for an analysis when you know how the choices will affect the results, because you know the effect in each of the trials one has. He also ignored the statistical problem of multiplicity—choosing to focus on 'findings' for particular tumor types, while ignoring other tumor types that failed to support his view. He ignored all of the relevant reviews by these staff and fellow medical officers.

Dr. Marciniak also failed to justify his determinations of cancer cases over the applicants', which is contrary to CDER policy, and failed to show the impact of his attributions on the final results. Moreover, when reviewers have attempted to verify the numbers of cancer-related adverse events that Dr. Marciniak found in various trials, they have been unable to corroborate his findings.

With respect to integration of data across multiple studies, Dr. Marciniak failed to justify his inclusion of some studies and rejection of others. He names factors in his decisions to exclude some studies that are highly unlikely to bias the results, giving the strong impression that he simply cherry-picked studies that supported his preferred conclusion.

Dr. Marciniak lists his own component reviews[44] of some of these studies, so we, his supervisors, were well aware of his interests in cancer-causing potential of various drug classes. We have discussed these matters with him on numerous occasions over the years, just not this final summary review. Dr. Marciniak had opportunities, therefore, to convey his point of view, and to hear and to respond to many of the criticisms we provide here, so we are puzzled that he provides so little insight into these other points of view. We also know that, having failed to convince us of a problem, Dr. Marciniak knew about the CDER appeal process, but he failed to avail himself of it. Instead, Dr. Marciniak ignored his colleagues and normal processes and planted this poorly argued case in various applications.

[44] *Page 62.*

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/s/

NORMAN L STOCKBRIDGE
11/13/2015

MARY R SOUTHWORTH
11/13/2015

ROBERT TEMPLE
11/13/2015

ELLIS F UNGER
11/13/2015

CLINICAL REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: December 17, 2014

Reviewer: Thomas A. Marciniak, M.D.
Cross-Discipline Team Leader (CDTL)

NDA: 206-143

Drug: ivabradine (Corlanor)

Subject: Cancer risk

Summary and Recommendations

Both the primary clinical reviewers and I have recommended approval of ivabradine for its heart failure (HF) indication, although with slightly different recommendations for the specifics of the indication. I judge that the combination of the primary clinical review and my CDTL review address well the major efficacy and safety issues relevant to approval. However, there is one important issue that, while addressed briefly in the primary clinical review, deserves more attention: cancer risk with ivabradine. I believe that cancer risk should always be an issue of special concern for any drug to be taken chronically. To justify that belief—and to provide background on some of the issues regarding the ascertainment of cancer risk in cardiovascular (CV) trials—I have included as an Attachment reviews documenting the cancer risks with three other classes of CV drugs, i.e., angiotensin receptor blockers (ARBs), antiplatelet drugs, and anticoagulants. Cancer risk is also a special concern for ivabradine because one non-U.S. regulatory authority has itemized incidence of cancer in the SHIFT trial as one of its safety concerns for ivabradine. Hence I address the cancer findings in all three of the ivabradine CV outcome trials in this review.

The cancer findings in the ivabradine CV outcome trials do not suggest that ivabradine increases the risk of any cancers. While there are numeric imbalances in cancer counts for some sites in SHIFT, the imbalances are not statistically significant and not repeated in the other trials. For imbalances that are suggestive or confirmatory of a drug increasing cancer risk please see the analyses in the Attachment.

I recommend the following:

1. These data do not change my recommendation for approval.

2. I do not recommend any special studies for ivabradine regarding cancer risks. However, if the sponsor does conduct any additional CV outcome studies, I recommend collecting cancer events as events of special interest as described in the Attachment. My justification for this latter recommendation is that, while SHIFT, BEAUTIFUL, and SIGNIFY results do not suggest a cancer risk, because they did not collect cancer data completely we cannot conclude absolutely that there is no risk.

3. The FDA should analyze cancer events in all outcome studies, including any submissions for new HF drugs.

Cancer Findings in the Ivabradine CV Outcome Trials

For the evaluation of cancers in the ivabradine CV outcome trials I used the methodology I had developed for the analysis of ARBs and cancer. I have included in the Attachment the description of that methodology as the last Appendix 6. Please see that appendix for the details. For the reasons discussed there I believe it is informative to analyze non-melanoma skin cancers, other solid cancers, brain tumors, and hematologic malignancies separately. I show the cancer findings in the ivabradine CV outcome trials in Table 1.

Table 1: First Cancer Events by Treatment Arm in the Ivabradine CV Outcome Trials

	SHIFT		BEAUTIFUL		SIGNIFY	
primary site	placebo	ivabradine	placebo	ivabradine	placebo	ivabradine
anus	0	0	0	0	0	1
bile duct	1	1	3	1	4	1
bladder	2	2	6	5	26	25
breast	4	3	3	1	12	8
carcinoid	0	0	0	0	0	1
cervix	2	1	0	1	3	1
colon	7	8	23	15	35	35
esophagus	0	2	4	3	3	4
gi other	1	0	0	1	0	3
head & neck	2	4	6	3	13	14
kidney	4	5	8	3	11	17
liver	2	2	0	2	1	7
lung	8	15	30	31	62	48
melanoma	1	0	5	4	7	4
mesothelioma	0	0	1	0	2	3
other	0	0	0	1	1	2
ovary	0	0	0	0	3	0
pancreas	3	1	2	5	16	11

primary site	SHIFT		BEAUTIFUL		SIGNIFY	
	placebo	ivabradine	placebo	ivabradine	placebo	ivabradine
penis	0	0	0	1	1	0
prostate	10	5	15	16	31	48
sarcoma	0	0	2	2	1	0
stomach	4	4	4	8	17	17
thyroid	1	0	0	0	1	1
unknown	3	3	4	7	9	8
uterus	0	1	0	1	3	3
vulva	0	0	0	0	2	1
solid cancer	55	57	116	111	262	261
non-melanoma skin cancer	3	9	14	15	38	38
brain tumor	1	2	2	4	12	8*
leukemia	2	3	2	0	2	5
lymphoma	1	0	4	4	8	6
myelodysplasia	1	1	5	1	3	7
myeloma	0	0	0	1	3	3
hematologic malignancy	4	4	11	6	16	21

* including 2 pituitary adenomas

The numbers in Table 1 are the counts of patients with a first cancer adverse event for the primary sites listed. The counts are for first events by the four categories in the double height rows, i.e., solid cancers, non-melanoma skin cancers, brain tumors, and hematologic malignancies. Hence it is possible, although rare, for a patient to be counted both as a solid cancer and a skin cancer or a solid cancer and a hematologic malignancy, etc. Furthermore, the counts are for first cancer events, not for the first diagnosis of a malignancy. In CV outcome trials in general, and in these trials, the vast majority of events are new diagnoses (with the exception of skin cancers.) Finally, because AE reports may not provide the malignancy status of brain tumors, the brain tumors include all brain tumors regardless of malignancy status and the count of 8 for the ivabradine arm of SIGNIFY includes two patients with pituitary adenomas.

The first cancer event counts by primary site appear to be equally distributed between the ivabradine and placebo arms, particularly considering all three trials together. While lung cancers and non-melanoma skin cancers were more frequent in the ivabradine arm than the placebo arm of SHIFT, these imbalances are not statistically significantly different and are not repeated in the other two studies.

COMMENT: I do not see a pattern of increased malignancies or brain tumors with ivabradine regardless of primary site. For examples of patterns that are suggestive or confirmatory of drugs that increase cancer risk, please see the analyses in the Attachment.

CLINICAL REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date:	December 12, 2014
Reviewer:	Thomas A. Marciniak, M.D. Medical Team Leader
NDAs:	20-839, 22-307, 22-433, 204-886, 9-218, 21-686, 22-512, 202-155, 202-439, and 206-316
TSI:	1361
Drugs:	Antiplatelet and anticoagulant drugs (clopidogrel, prasugrel, ticagrelor, vorapaxar, warfarin, ximelagatran, dabigatran, apixaban, rivaroxaban, and edoxaban)
Subject:	Cancer risk

Summary

The large outcome trial supporting the approval of prasugrel, the first new antiplatelet drug approved in more than 10 years, raised the issue of whether use of a drug inhibiting coagulation could be associated with an increased risk of solid cancers. (Marciniak 2009) Subsequent trials of antiplatelet and anticoagulant drugs provided both supportive and neutral evidence for this association. The most recent submission for a new anticoagulant, edoxaban, is typical in providing, by itself, suggestive but not conclusive evidence for the association. (See **ENGAGE** below.) However, the most recently reported trial, the Dual Antiplatelet Therapy (DAPT) Study, provides strong evidence that the association of use of drugs inhibiting coagulation with an increased risk of solid cancers is real.

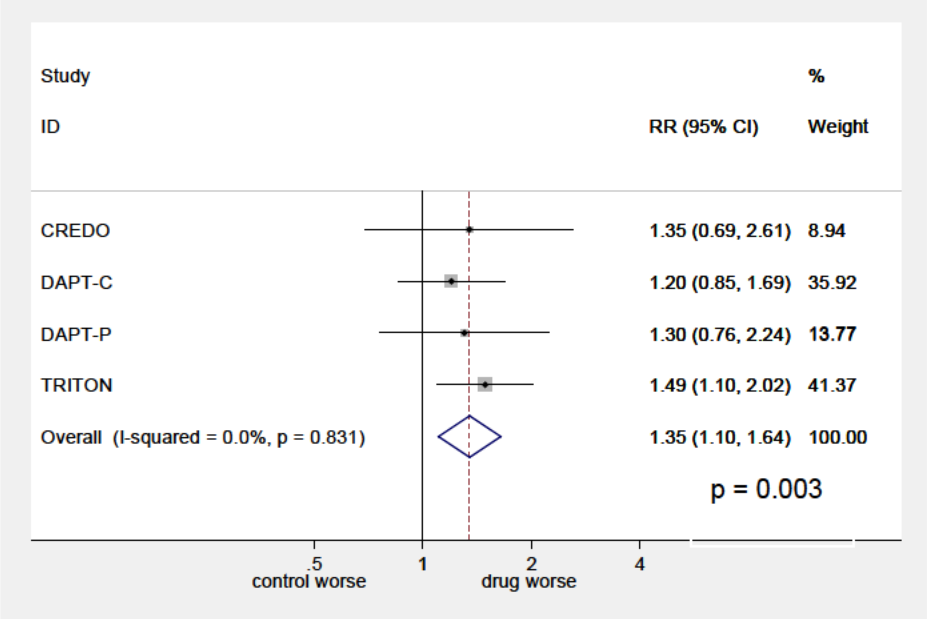
DAPT is a large (N = 11,648), randomized, placebo-controlled trial comparing 30 vs. 12 months of dual antiplatelet therapy in coronary stented patients. In August 2014 the principal investigators shared with the FDA the preliminary results: While the 30-month arm did have lower rates for the primary death, myocardial infarction (MI), or stroke (MACCE) endpoint and for stent thromboses, it had a higher rate of all cause mortality in the drug-eluting stent subgroup (hazard ratio (HR) (b) (4) p = 0.04) and had higher rates of cancer (HR (b) (4)) and cancer deaths (b) (4) in the whole study. (See Attachment 1.) The latter findings, both the mortality and the cancer results, have generated considerable concern among the investigators, the sponsors, and the FDA. The Division Deputy Director for Safety filed a memo concluding that the finding of increased mortality is reliable and that "the number of non-

cardiovascular deaths are also certain." (Southworth 2014) Regarding cancers the memo states that "Cause of death may be less certain and therefore some thought must go into how/if the cancer and trauma death findings would be represented in the [safety] communication." Because I have analyzed cancer and non-CV death findings in all large antiplatelet and anticoagulant studies submitted to the FDA, I am filing this review to record the cancer findings for edoxaban and to provide data-based recommendations for addressing the serious issue of cancer risk with all drugs that inhibit coagulation.

DAPT results support an increased risk of solid cancers with thienopyridine use, at least in the setting of invasive percutaneous procedures. The DAPT results look like an extension of the prasugrel TRITON study, the index study that raised the issue of whether the thienopyridine prasugrel increases solid cancer rates. In TRITON, like in DAPT, the arm with greater thienopyridine effect had more bleeding, more solid cancers, and more non-CV deaths.

The consistency of these relationships is shown well by a meta-analysis of solid cancer events in the thienopyridine outcome trials with substantial invasive approach in which cancer data were collected and for which the FDA has the trial data. I show the meta-analysis results in Figure 1.

Figure 1: Meta-Analysis of Solid Cancer Events in the Thienopyridine Trials with Substantial Invasive Approach and for Which the FDA Has Cancer Data



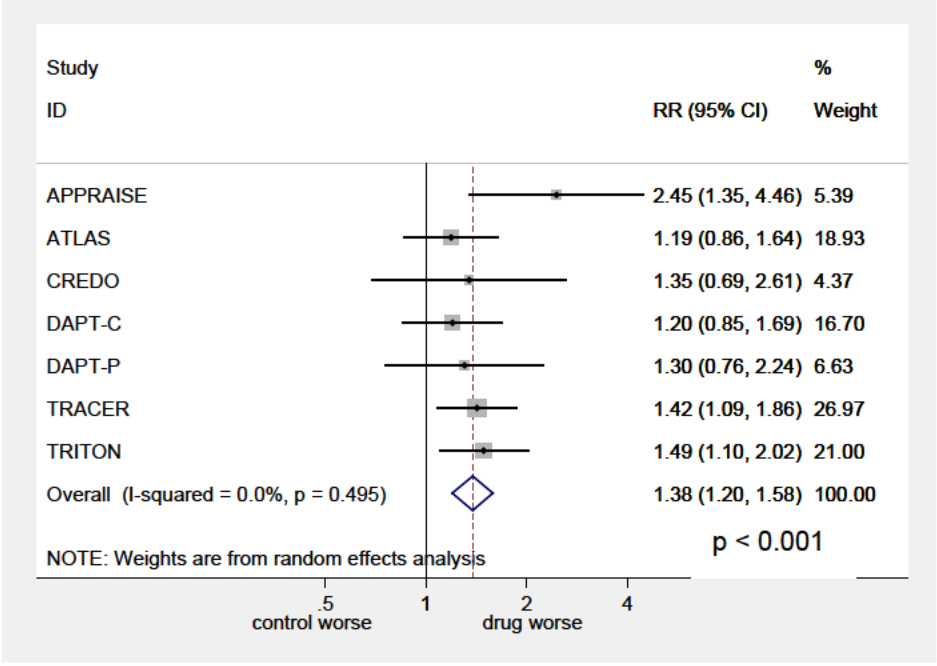
DAPT-C in Figure 1 is the clopidogrel substudy of DAPT and DAPT-P is the prasugrel substudy. All four studies are remarkably consistent for solid cancer risks.

In addition to the thienopyridine trials, there have been two recent large outcome trials in predominantly invasive ACS patients of non-thienopyridine antiplatelet drugs: PLATO for the non-thienopyridine $P2Y_{12}$ receptor inhibitor ticagrelor and TRACER for the PAR-1 receptor inhibitor vorapaxar. The TRACER results are very similar to those shown in Figure 1; including them changes the RR minimally (1.37) but reduces the p value to < 0.001. PLATO did not show an increased rate of solid cancers with ticagrelor but its bleeding RRs are close to 1, study

duration was relatively short, and it had serious conduct problems that challenge its validity. Including both TRACER and PLATO in the meta-analysis produces a pooled RR estimate of 1.24 and a p value of 0.002.

There have also been two recent large, placebo-controlled outcome trials of new oral anticoagulants (NOACs) in predominantly invasive ACS patients: APPRAISE for the factor Xa inhibitor apixaban and ATLAS for the factor Xa inhibitor rivaroxaban. Both of these NOAC outcome trials in ACS support an association between increased bleeding and solid cancers. The solid cancer results in APPRAISE, which had substantially higher bleeding rates in the apixaban arm, are statistically significant ($p = 0.003$) for APPRAISE alone. In rivaroxaban ATLAS the solid cancer results are not statistically significant. However, ATLAS tested two doses and there is a strong suggestion for a dose-response both for bleeding and for solid cancers. I performed a random effects meta-analysis of solid cancer events combing these two NOAC trials and the invasive antiplatelet drug trials (all of which have major bleed risk ratios ≥ 1.2). I show the results in Figure 2.

Figure 2: Meta-Analysis of Solid Cancer Events in the Antiplatelet and Anticoagulant Trials with Substantial Invasive Approach and Having a Major Bleed RR ≥ 1.2 and for Which the FDA Has Cancer Data



The p value for the DerSimonian-Laird random effects meta-analysis in Figure 2 is <0.001. If PLATO (which has a lower major bleed RR as well as conduct problems) is included in the meta-analysis, the p value is 0.004.

Survival following a solid cancer event was typically poor in all studies and similar between the drug and control arms. In the DAPT the difference in malignancy deaths was high enough to result in an appreciable difference in non-CV deaths. I show in Figure 3 a meta-analysis of non-CV mortality for the same trials include in Figure 2 and in Figure 4 a meta-analysis of deaths in patients with solid patients with solid cancers.

Figure 3: Meta-Analysis of Non-CV Mortality in the Antiplatelet and Anticoagulant Trials with Substantial Invasive Approach and Having a Major Bleed RR ≥ 1.2 and for Which the FDA Has Cancer Data

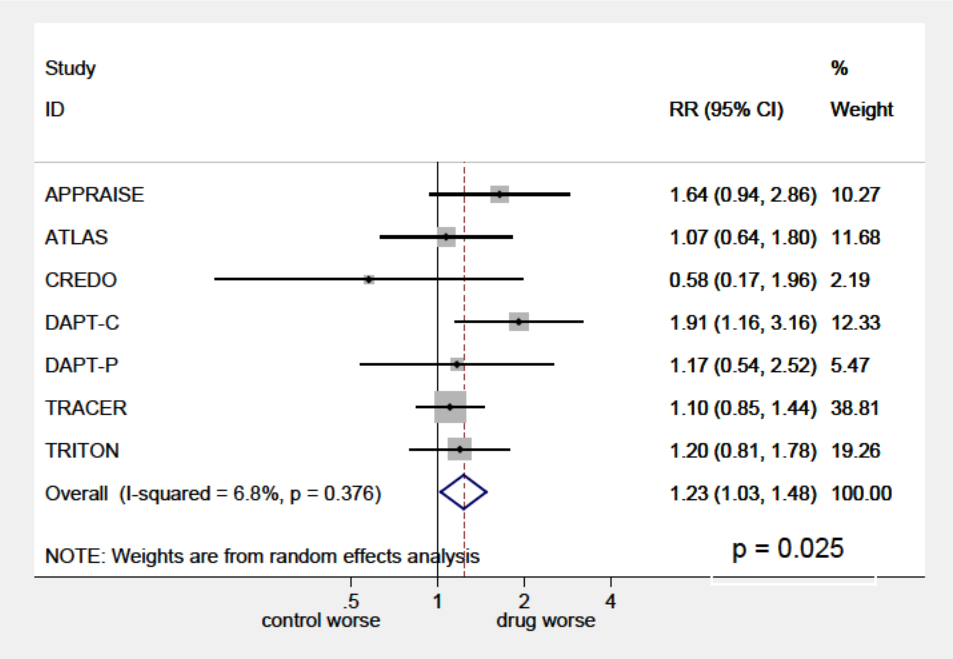
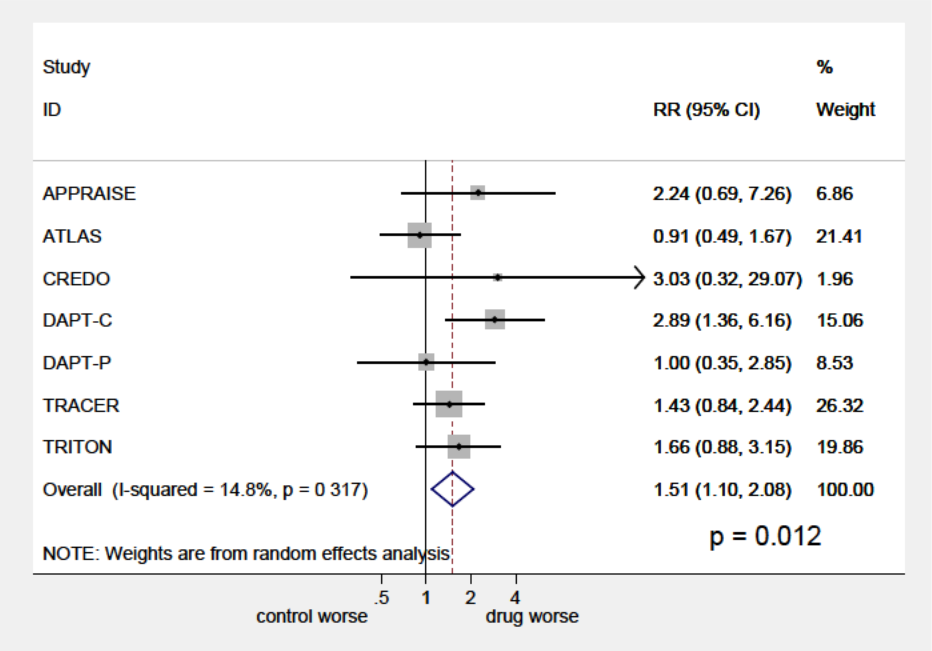


Figure 4: Meta-Analysis of Deaths in Patients with Solid Cancers in the Antiplatelet and Anticoagulant Trials with Substantial Invasive Approach and Having a Major Bleed RR ≥ 1.2 and for Which the FDA Has Cancer Data



The trials statistics used to produce Figure 4 for all trials except DAPT are the deaths during the trial ITT period for all patients having a solid cancer event reported during the ITT period. (In the tables of trials at the start of each drug and cancer section below the rows "Died %, solid ca pts (control)" provides this statistic for the control arms.) For DAPT they are the adjudicated malignancy deaths because that is the statistic reported. Both figures confirm that the increased solid cancers observed in the trials result in more deaths. The variability is higher for these cause-specific mortality statistics than for solid cancer rates because the numbers of cause-specific deaths are lower than the numbers of solid cancers. The mortality rates in the patients with solid cancers range from about 3- (in a short study) to 8-fold higher than the mortality rates in patients who didn't experience a solid cancer event. Because solid cancers are deadly, I advocate analyzing deaths in patients with solid cancers to avoid the problems of adjudication and arbitrary decisions about the underlying causes of deaths.

The results of the antiplatelet drug trials without a substantial invasive approach contrast with those shown in Figure 2. The older non-invasive clopidogrel trial results do not support a relationship between clopidogrel use or bleeding and solid cancers. All trials had study limitations that I discuss in the **Clopidogrel and Cancer** section that limit their validity. Prasugrel TRILOGY in medically managed ACS is similarly negative, although TRILOGY, like PLATO, had serious conduct problems. Vorapaxar TRA2P, a very large trial in high risk patients, was neutral for solid cancers and non-CV deaths despite substantially higher bleeding in the vorapaxar arm. However, TRA2P had a design flaw similar to the ones in the two large clopidogrel studies (CAPRIE and CHARISMA) that also produced neutral results: CAPRIE did not count adverse events (AEs) more than 28 days after study drug discontinuation; CHARISMA defined AEs as occurring within 28 days of treatment discontinuation; and TRA2P did not solicit AEs that occurred more than 60 days after the last dose. While these restrictions may not appear to be too limiting, I have a well-documented experience with another outcome trial that suggests that their impact may be critical:

> The LIFE study was a large trial of losartan vs. atenolol in hypertensive patients with left ventricular hypertrophy. The sponsor of LIFE counted AEs only until 14 days after study drug discontinuation (although they collected AEs throughout the trial.) Applying the 14 day limit atrial fibrillation (afib) SAEs were similar in the two arms (2.0% vs. 2.1%, atenolol vs. losartan) and numerically higher with losartan. However, I demonstrated that AE rates did not return to a stable level until about 90 days after study drug discontinuation. Counting AEs until 90 days after study drug discontinuation I could document a small difference in afib AE rates between the two arms (7.9% vs. 6.8%, atenolol vs. losartan), higher with atenolol. While this small difference in afib rates would not appear to be critical, Minnesota coding of annual ECGs collected in LIFE confirmed a difference in afib rates favoring losartan (7.9% vs. 5.7%). These differences, again not alarming, were impactful: Losartan was superior to atenolol in LIFE for stroke rates. The detected difference in afib rates accounted for half of this difference in stroke rates.

I have concerns that investigators interpreted limits on AEs such as 28 days or 60 days after treatment as indicating that only AEs clearly related to the study drug should be collected—and investigators would not consider cancer to be related to these drugs. I suspect that the neutral results in CHARISMA and TRA2P may be related to their AE collection specifications.

That how AEs are or are not collected can affect cancer findings is demonstrated well by analyses of the angiotensin receptor blocker (ARB) trials for cancer. (Marciniak 2013) Because the analyses are extensive and highly relevant to this review, I have included the ARB trials analyses as Attachment 5. Please see Appendix 1 of that attachment for a detailed discussion of trials for which AE collection deficiencies led to inadequate cancer ascertainment. Please see Attachment 6 the pre-specified methodology that I used for the analyses of cancer in the ARB, antiplatelet, and anticoagulant trials. (Marciniak 2012) For both ARBs and drugs inhibiting coagulation, the trials having reasonably complete AE collection show an association between drug use and cancer risk. (For ARBs the risk is for lung cancer, not all solid cancers.) The trials with incomplete AE collection frequently fail to show the association.

We should also consider possible mechanistic differences between invasive and non-invasive of trials. One possibility is the use of drug eluting stents (DES) in the invasive trials. DAPT may raise this issue because the differences in non-CV deaths and adjudicated malignancy deaths (per the preliminary presentations) occur only in the DES subgroup—these statistics in the bare metal stent (BMS) subgroup are similar between arms. However, the BMS subgroup is about $1/6^{th}$ the size of the DES group so its event rates are low and hence their confidence intervals are wide. The older trials do not support an effect of DES on solid cancer rates. CREDO was conducted prior to the introduction of DES. The trials with DES use (TRITON, ATLAS, APPRAISE, and TRACER) do not show an increased risk of solid cancers with DES use or an interaction between DES and drug for solid cancer incidence. Furthermore, for the trials including more balanced numbers of invasive and medically managed patients (ATLAS, APPRAISE, and TRACER), there are no significant differences in cancer risk between the invasive and medically managed patients nor is there a significant interaction between invasive management and drug use for cancer risk.

There could be other biologic mechanistic differences between the two sets of trials (e.g., radiation exposure from cardiac fluoroscopy in the invasive trials?) but my suspicion remains that the different solid cancer findings in the two sets of trials are related to cancer ascertainment limitations in the noninvasive trials. I do not know of a method for proving that hypothesis with the existing data (but I do recommend changes for future trial conduct in the next subsection.) I remain highly concerned about the bleeding and cancer associations in the invasive trials and the mortality findings in SPS3, the NIH trial of clopidogrel and aspirin vs. aspirin alone in recent stroke. Unfortunately we do not have cancer data for SPS3. SPS3 again suggests that clopidogrel can produce more bleeding and more non-CV mortality. While our expectation is that the high non-CV mortality in SPS3 is related to cancer (the publication states that it is not related to bleeding), confirmation of that would be informative.

The anticoagulant trials provide some additional insights: Apixaban APPRAISE in ACS provides an informative comparison to apixaban ARISTOTLE in afib. While in APPRAISE there was more bleeding with apixaban (because it was administered on a background of DAPT) and more solid cancers, in ARISTOTLE there was less bleeding with apixaban and fewer solid cancers. In ARISTOTLE warfarin showed a higher rate of solid cancers. The difference in cancers is borderline significant ($p = 0.052$ by log rank) for the ITT period and nominally significant ($p=0.024$) for all cancers reported. The ximelagatran SPORTIF V trial also shows higher bleeding rates and higher solid cancer rates with warfarin. ARISTOTLE and SPORTIF V demonstrate that the cancer increases appear to be related to inhibition of the coagulation system,

not strictly related to a particular receptor or to platelet inhibition, and that warfarin is implicated as well as the NOACs.

Other anticoagulant trials suggest another complexity: The cancer effects may be related to specific tissue concentrations and not systemic blood levels. Many of the NOACs show increased GI bleeding rates despite having overall bleeding rates lower than warfarin's. While colon cancer[1] has variable results in the trials, four of the trials show increased rates of esophagus cancer in the NOAC arms: dabigatran RELY; edoxaban ENGAGE; and ximelagatran SPORTIF III and V. (Rivaroxaban ATLAS also reported esophagus cancers in its two rivaroxaban arms, but only one in each of the arms.) Many of these esophagus cancers were reported late, suggesting that an early detection bias was not the mechanism. There are other variations in specific cancer site incidences between arms in the NOAC studies but, given that any specific site has small numbers of cancers reported for a given study, most of the variations are remote from statistical significance and impossible to sort out from chance variations.

For the NOACs, as for the antiplatelet drugs, the two studies (APPRAISE and ATLAS) with the highest bleed RRs and showing an association of bleeding with increased solid cancers were ACS studies with a substantial invasive component. These studies were also the placebo-controlled studies with the NOAC administered typically in addition to dual antiplatelet therapy, the latter contributing to the high bleed RRs. Only AVERROES (apixaban vs. aspirin) showed a slightly higher bleed RR for the NOAC and little difference in solid cancer rates. The other NOAC trials were warfarin-controlled and reported lower bleeding RRs for the NOACs than for warfarin, with only SPORTIF V suggesting an association between overall bleeding and overall solid cancer rates. The threshold for observing an increase in solid cancer rates in the NOAC trials of these sizes appears to be at least a major bleeding RR of 1.4 (the RR for warfarin/NOAC in SPORTIF V.)

I have mentioned an "early detection" effect or bias several times. Some have tried to explain the prasugrel TRITON and other trial results as totally the result of early detection resulting from investigations of bleeding. However, several observations argue against that conclusion:

- Survival after a solid cancer event is typically poor and equally poor regardless of the imbalance in events. If there were a detection bias, we would expect at least a lead-time bias because of the earlier detection and hopefully improved survival—the latter is why we advocate cancer screening! That survival may be worse is shown in DAPT by the fact that the statistically significant signal is for non-CV mortality rather than for solid cancer incidence.
- The overall solid cancer incidence curves do not typically diverge immediately but only after a delay of several months. They also typically diverge for the duration of the studies.

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[1] [1] In this review I refer to "colon cancer". I include rectal carcinomas with colon carcinomas in the term "colon cancer."

- For some sites for which bleeding is a telltale sign (e.g., colon, other GI, bladder), we do see an initial diagnosis of a few cases immediately after randomization. The initial high rate of diagnosis is not typically sustained beyond a few months.
- DAPT provides the strongest argument against an early detection bias. DAPT randomized patients at one year after initiating thienopyridine treatment, after the time we would expect an early detection bias to have dissipated. The early high detection rates for the incidence curves suggesting a detection bias typically last only a few months.

I conclude that the totality of evidence strongly supports that prolonged thienopyridine use is associated with increased rates of solid cancers, at least in patients undergoing invasive procedures. The evidence also suggests that the association is not limited to inhibition of the $P2Y_{12}$ receptor but extends to the PAR-1 receptor. The totality of evidence also supports that excess bleeding from higher anticoagulant dosing also increases the risk of solid cancers. Hence the increased solid cancer risk appears to be related to inhibition of coagulation and not inhibition of a particular receptor or use of a particular drug, i.e., it is a "class" effect. I provide recommendations below based on these conclusions as well as my observations regarding trial conduct problems in the 23 trials analyzed.

Recommendations

1. The FDA should provide practitioners and patients with the data regarding the association between bleeding and solid cancers **as soon as possible**. The increased deaths and solid cancers in DAPT, consistent with other antiplatelet trials with a predominantly invasive approach, justify immediate action. The FDA safety communication from November 16, 2014, that advises patients and practitioners to continue DAPT bases that advice on flawed logic: It reports that more patients on extended DAPT died, the outcome of prime importance, but concludes that the benefit-risk for extended DAPT is still favorable. (FDA 2014) The current FDA plan for resolving the DAPT cancer risk issue, outlined in minutes from an internal meeting, has a proposed schedule that is completely inappropriate for the seriousness of this issue: "The goal date for CDER's review will be 6 months from the time the data from DAPT are submitted." (Wachter and Southworth 2014) The FDA plan appears to be dismissing cancer risk with antiplatelet drugs as unimportant just as it suppressed the evidence associating ARBs with lung cancer: Almost five years after the association of ARB use with cancer was first published (Sipahi, Debanne et al. 2010), the FDA still has not released the evidence that the risk of lung cancer with ARB use is real.
2. There are at least two possible approaches for conveying this critical information regarding the risks of long term DAPT:
    a. The issuance of a safety communication summarizing the findings in this review along with the posting of this review on the FDA website.
    b. The holding of an advisory committee meeting on this topic and the related topic of angiotensin receptor blockers (ARBs) and cancer, with the usual public posting

of this review and all of the ARBs and cancer documents immediately prior to the meeting.

3. The FDA should review all of the data regarding duration of dual antiplatelet therapy post-stenting and integrate it with these data regarding bleeding and cancer. Based on this review the FDA should recommend changes to the labels of antiplatelet drugs to include warnings regarding solid cancers and recommendations for duration of antiplatelet therapy and for investigating possible cancer signals. The FDA should also recommend changes to the labels of anticoagulants noting the data regarding anticoagulants and cancer and including recommendations for investigating possible cancer signals.
4. The FDA should inform the sponsors about the signal for esophagus cancers with NOACs, request their proposals for elucidating it, and design or commission drug surveillance database studies to address the signal.
5. Our confidence in the trial results and our understanding of the differing results between the invasive and non-invasive trials is reduced by trial conduct issues, particularly incomplete follow-up and limitations in adverse event reporting. These trial conduct issue are not limited to the question of bleeding and cancer but are pervasive for all recent trials and for all issues. The FDA should inform sponsors about the following expectations:
    a. Vital status ascertainment in trials should be > 99% of all randomized subjects. All trials should capture the identifiers needed for national death registry indexing. If regions refuse to allow passive follow-up of vital status for trial subjects, e.g., registry access, then the trial sponsor should not conduct trials for U.S. registration in those regions.
    b. The FDA should inform sponsors that knowing subjects didn't have certain events by the end of the study—not the end of treatment or the end of treatment plus an finite period—is as critical as knowing that subjects did have certain events. Cancer is always one of these events of special interest—see the next item for specific recommendations regarding cancers. Besides deaths major cardiovascular adverse events, including MIs, strokes, and other major thrombotic events, are also always events of special interest. The sponsor should design trial procedures and case report forms (CRFs) to ensure the following:
        i. Preferably all living trial subjects should have a final site visit on or after the global trial end date, although final phone contacts may be allowed for subjects who have discontinued treatment. Site staff should follow a detailed written protocol for conducting the site visits, including the date of contact, the site staff conducting the visit or contact, whether the patient visited or was contacted, the relationship of the contact to the patient if not the patient, and specific questions regarding not only the endpoint events but all adverse events of special interest. The CRFs for visits should be recorded and submitted in real time, not days or weeks later.

ii. The completion rate for subjects with a well-documented site visit or contact on or after the global trial end date should be > (100%-1% x years from randomization). This goal, like the >99% for vital status, is not meant to be a rejection criterion. If it is achieved, then the burden of proof will rest with the FDA to show that the study is unreliable if there is other evidence of problems, e.g., from inspections. If it is not achieved, then the burden of proof will be on the sponsor to convince the FDA that the study is reliable.

6. The FDA and sponsors must recognize that pre-clinical rodent carcinogenicity are inadequate for detecting cancer promoting drugs. One mechanism for understanding better the cancer promotion potential of drugs having large outcome trials is to record malignancies accurately and completely in such trials. Hence malignancies, other than basal cell and squamous cell skin cancers, should be considered events of special interest to be captured for the entire duration of such trials regardless of treatment discontinuation. The protocol and site manuals should specify following up on all potential malignancy events (e.g., unexplained GI bleeds, lung nodules) until the malignancy status of them is determined. For all malignancies the protocol and site manuals should specify collecting the operative report for the diagnosis, the histopathology report for the diagnosis, the presumed primary site (if the operative report and the histopathology report were not done or are not available or do not identify the primary site), the date of first clinical diagnosis of the malignancy event, and (for the patients with malignancy events) the identities of all malignancies diagnosed prior to randomization, and the current statuses of all know malignancies.

DAPT Study Results

The principal investigators published the rationale and design for the DAPT study. (Mauri, Kereiakes et al. 2010) They stated that the study was sponsored by Harvard Clinical Research Institution and they acknowledged four drug eluting stent (DES) manufacturers and four thienopyridine manufacturers as providing funding for the study, as well as supplemental funding from Health and Human Services. They described the aim of DAPT as ascertaining the impact of extending the duration of dual antiplatelet therapy beyond 1 year after coronary stent procedures by examining the balance of risk and benefit in a broad population of treated patients.

To achieve this aim they proposed a novel study design: Patients undergoing percutaneous coronary intervention (PCI) with stent placement (15,245 DES patients and 5,400 bare metal stent (BMS) patients) and no contraindications to long term DAPT and no current medical conditions with a life expectancy < 3 years were to be enrolled at the time of PCI. The enrolled patients were to receive 12 months of open label DAPT, with the choice and dosage of the thienopyridine (clopidogrel or prasugrel) left to local investigator choice. Aspirin dosage was to be the lowest acceptable dose per physician's discretion (75-325 mg for the first 6 months after the procedure and 75-162 mg indefinitely thereafter.) All enrolled patients who were treated for 12 months with DAPT and who were event-free (from death, MI, stroke, repeat coronary revascularization, stent thrombosis, and GUSTO moderate or severe bleeding) and who demonstrated compliance with thienopyridine therapy (defined as no interruptions > 14 days) were eligible for randomization. Eligible patients were to be randomized to continue

thienopyridine treatment (at the pre-randomization dosage of clopidogrel 75 mg or prasugrel 5 or 10 mg daily) or to placebo, while continuing aspirin, for an additional 18 months. Study drug was to be discontinued at 30 months followed by a 3-month observation period with patients on aspirin alone (to capture possible thienopyridine withdrawal rebound events.) The co-primary efficacy endpoints at 33 months were to be MACCE and stent thrombosis. The primary analyses were to be performed on the DES patients.

The investigators presented the preliminary results to the FDA in four PowerPoint presentations. (DAPT_Investigators 2014; DAPT_Investigators 2014; DAPT_Investigators 2014; DAPT_Investigators 2014)[2] and recently published the main trial results for the DES subgroup. (Mauri, Kereiakes et al. 2014) The preliminary communications and PowerPoint presentations do not provide all of the details helpful for understanding the study results, e.g., they do not include detailed reasons for enrolled patients not being randomized, dosages for prasugrel and aspirin, follow-up details, etc. The NEJM publication included statistics based on readjudication for malignancies and malignancy deaths but did not change appreciably the cancer statistics from the preliminary presentations. What has been reported remains very concerning. I summarize the data presented relevant to the mortality and cancer findings below.

I show in Table 1 the patient flow in DAPT.

Table 1: Patient Flow in DAPT

	DES		BMS	
	N	%	N	%
Enrolled	22,866		2,816	
Randomized	9,961	44%*	1,687	60%*
30m follow-up	9490	95%†	1580	94%†
33m follow-up	9390	94%†	1565	93%†

*percent of enrolled; †percent of randomized

The number enrolled is substantially higher than that projected in the 2010 article for DES but lower for BMS. Note that only about 44% of patients in the DES subgroup were randomized while only 60% of patients in the BMS subgroup were randomized. The presentation slides did not specify how the follow-up statistics count deaths but another presentation slide shows about 5% missing data, so presumably the statistics in Table 1 count deaths as non-missing.

COMMENT: How enrolled patients were selected for randomization could affect the cancer risks, but it is impossible to project how or the magnitude of any effect. Regardless, because DAPT was a large randomized trial, the initial risks should be equal in both arms. We should be aware of the unique study design, i.e., the 1-year "run-in" period with about half of patients excluded, when comparing DAPT to the typical antiplatelet study lacking the extended run-in. It is also relevant whether the randomization rates varied by thienopyridine type, i.e., clopidogrel

[2] Because the PowerPoint presentations provide the data on which I based my analyses of DAPT and because the investigators have not published many of those data, I have included the presentations as Attachments 1 to 4.

vs. prasugrel, but that information was not provided in the two preliminary communications. The rate of missing data, about 5-6%, appears to be neither great nor incomplete enough to reject the study results

Because the focus of this review is upon cancer risk and mortality, not efficacy, I will not provide details of the preliminary efficacy analyses. The presentations provide conclusions that, for the primary DES analysis, 30m DAPT was associated with reduction in both MACCE and stent thrombosis at 30 and 33m. The benefit was greater for stent thrombosis (HR 0.29) than for MACCE (HR 0.71). The MACCE benefit was driven by reduction in MI.

Despite the reported benefit for stent thrombosis and MI, all cause mortality trended (b) (4) The two preliminary presentations and the NEJM publication did not have statistics for the study as a whole but did include the following Kaplan-Meier (K-M) plot for the DES subgroup.

Figure 5:

While cardiovascular (CV) death rates were neutral, non-CV deaths (NCVD) diverged starting at about 6 months post randomization as shown in the following K-M plot.

Figure 6:

COMMENT: The cause of death (b) (4) *in non-CV deaths for a moderate-sized study such as DAPT should be obvious. I show in Table 2 the CDC's tabulation of the causes of death in the 2011 U.S. population aged 60-64 (the average age in DAPT was about 62): (CDC 2014)*

Table 2: CDC Causes of Death in the 2011 U.S. Population Aged 60-64

	Cause of death (ICD-10)	N	% NCVD
	All causes	179,043	
	All non-CV deaths (NCVD)	131,142	100%
1	Malignant neoplasms (C00-C97)	64,649	49%
2	Diseases of heart (I00-I09,I11,I13,I20-I51)	39,152	
3	Chronic lower respiratory diseases (J40-J47)	9,381	7%
4	Diabetes mellitus (E10-E14)	7,249	6%
5	Accidents (unintentional injuries) (V01-X59,Y85-Y86)	6,602	5%
6	Cerebrovascular diseases (I60-I69)	6,509	

	Cause of death (ICD-10)	N	% NCVD
7	Chronic liver disease and cirrhosis (K70,K73-K74)	4,888	4%
8	Nephritis, nephrotic syndrome and nephrosis (N00-N07,N17-N19,N25-N27)	2,857	2%
9	Septicemia (A40-A41)	2,812	2%
10	Intentional self-harm (suicide) (*U03,X60-X84,Y87.0)	2,713	2%
11	Influenza and pneumonia (J09-J18)	2,365	2%
12	Essential hypertension and hypertensive renal disease (I10,I12,I15)	1,500	
13	Viral hepatitis (B15-B19)	1,427	1%
14	In situ neoplasms, benign neoplasms and neoplasms of uncertain or unknown behavior (D00-D48)	886	1%
15	Aortic aneurysm and dissection (I71)	740	
	All other causes (Residual)	25,313	19%

Note that about 50% of the non-CV deaths were attributed to cancer while the highest percentage of another non-CV specific cause of death (lower respiratory disease) is 7%. Given that it is mechanistically improbable that a drug causes a difference in all non-CV causes of death, for a moderate-sized drug study to show a significant difference in non-CV deaths there are two possibilities: (1) Either the drug causes a moderate increase in cancer deaths or (2) the drug causes a whopping increase in another specific cause of death. For example, for the second most frequent non-CV cause of death (lower respiratory disease at 7%) we can estimate the magnitude of the increase required as follows: (b) (4)

[redacted]

That an antiplatelet drug may increase the risk of cancer is an issue that I raised based on my reviews of the prasugrel TRITON study starting in 2008. For the details please seem my review dated May 6, 2009. (Marciniak 2009) I also reviewed the cancer findings in the prasugrel TRILOGY study in my review dated September 13, 2013. (Marciniak 2013) I have summarized the findings from both studies in the ***Prasugrel and Cancer*** *section below.*

My review of cancers in TRITON was motivated by my interpretation of the prasugrel mouse carcinogenicity study that prasugrel increased frequencies of solid cancers in mice. Based on that study and the arguments presented below I pre-specified performing the primary analyses for TRITON on solid cancers excluding non-melanoma skin cancers and brain tumors. My justifications for excluding from the primary analyses hematologic malignancies, non-melanoma skin cancers, and brain tumors are the following:

- *Hematologic malignancy rates were not increased by prasugrel in the mouse carcinogenicity study. Furthermore, one possible mechanism for an antiplatelet drug promoting solid cancers is interfering with platelet aggregation and hence interfering with a potential defense mechanism against solid cancer neovascularization. Hematologic malignancies are not dependent upon neovascularization.*

- *Non-melanoma skin cancers (more accurately basal cell and squamous cell skin cancers) are much less serious than other solid tumors and rarely metastasize or cause death. They are likely underreported in clinical trials, e.g., they are the most frequent cancers in the elderly in population studies but not in clinical trials. Furthermore, the underlying etiology is predominantly solar skin damage, an etiology not operative for other solid cancers.*

- *Brain tumors are dependent upon the drug crossing the blood-brain barrier. They are not infrequently reported as "brain tumors" without a histologic diagnosis and without a confirmation of malignancy. Not uncommonly they are not distinguished as primary tumors or metastatic disease.*

I believe these exclusions are still reasonable for the primary analyses of cancers associated with drugs causing bleeding. I present the statistics from the presentations for solid cancers below as well as for my three exclusions separately.

The presentations do not identify whether the statistics are for new diagnoses or for new malignancy events, including ones in patients with a history of a malignancy at the same site. With that limitation I show in Table 3 malignancies by site and thienopyridine use in DAPT months 12 to 33 as reported in the presentations.

Table 3: Malignancies by Site and Thienopyridine Use in DAPT 12-33m

	Clopidogrel		Prasugrel		Either	
Site	30m	12m	30m	12m	30m	12m
Bladder	5	4	3	0	8	4
Bone	2	0	0	0	2	0
Breast	2	8	3	1	5	9
Colorectal	8	8	5	4	13	12
Endocrine	1	2	0	2	1	4
Esophagus	1	2	0	3	1	5
Gynecologic	1	0	1	0	2	0
Kidney/Ureter	3	3	2	1	5	4
Liver	1	0	1	2	2	2
Lung	15	12	2	2	17	14
Malignant melanoma	1	4	0	0	1	4
Metastasis, primary?	12	6	0	1	12	7
Oral Cavity/Pharynx	0	1	2	2	2	3
Other	3	0	1	0	4	0
Pancreas	2	0	3	1	5	1
Prostate	14	9	7	3	21	12
Stomach	1	1	0	1	1	2
Solid cancers N	72	60	30	23	102	83
Solid cancers RR*	1.2		1.3		1.2	

Site	Clopidogrel		Prasugrel		Either	
	30m	12m	30m	12m	30m	12m
Brain	2	0	1	0	3	0
Non-melanoma skin	6	5	0	0	6	5
Leukemia	1	2	1	1	2	3
Lymphoma	4	1	2	2	6	3
Other hematologic	2	3	0	1	2	4
All hematologic	7	6	3	4	10	10

*RR = risk ratio 30m/12m

The increased risk of solid cancers with continued thienopyridine use is consistent between clopidogrel and prasugrel (risk ratio 1.2 vs. 1.3). There are higher rates of bladder, prostate, and pancreas cancers and unknown primaries in the 30m arm. GI cancers, ones whose detection we associate with bleeding, were not increased in the 30m arm.

Brain tumors were rare but were only reported in the 30m arm. Non-melanoma skin cancers were rarely reported (and likely unreported) and evenly distributed. Hematologic malignancies were also evenly distributed between the two arms.

This point estimate of the increased risk of solid cancers is not statistically significant ($p \sim 0.19$ by Chi square statistic) in DAPT but the study is underpowered for detecting a modest difference in cancer risk. If the point estimates of the rates are the true rates, about 54,000 patients would have to be randomized in order to have 80% power of detecting a risk ratio of 1.2 at alpha = 0.05.

While the difference in solid cancer rates is not statistically significant, the investigators reported a statistically significant difference in deaths attributed to cancer (33 vs. 16, $p = 0.02$.) As noted above, cancer deaths contributed substantially to the higher rate of non-CV death in the 30m arm.

COMMENT: While the increased solid cancer incidence in the 30m arm is not statistically significant, we should interpret it in light of the statistically significant difference in cancer deaths and in light of the cancer rates in other studies of antiplatelet drugs. The supporting evidence from these latter observations suggests that the increased solid incidence is real. I summarize the evidence from other studies of antiplatelet drugs below.

I have observed in other antiplatelet and anticoagulant studies that solid cancer rates frequently are higher in the arms with higher bleeding rates. GUSTO moderate/severe bleeding was the pre-specified primary safety endpoint in DAPT. Hence I show in Table 4 the GUSTO moderate/severe bleeding rates by thienopyridine use in DAPT, DES Subgroup, months 12-30.

Table 4: GUSTO Moderate/Severe Bleeding Rates by Thienopyridine Use in DAPT, DES Subgroup, Months 12 to 30

	clopidogrel	prasugrel	either
30m	2.66%	2.28%	2.5%
12m	1.68%	1.36%	1.6%
diff	0.98%	0.92%	0.96%
RR*	1.6	1.7	1.6
p	0.01	0.048	0.001

*RR = risk ratio 30m/12m

Bleeding was moderately increased with continued thienopyridine use. The increased relative risk was similar for clopidogrel and for prasugrel.

COMMENT: The increased bleeding and solid cancer rates are consistent with the increased bleeding and solid cancer rates we have seen with other antiplatelet and anticoagulant agents. Clopidogrel and prasugrel appear to have behaved similarly for both bleeding and solid cancers in DAPT. I am not concerned that only clopidogrel appears to have shown a difference for deaths attributed to cancer or for non-CV deaths because the prasugrel subgroup was smaller and its confidence intervals for such statistics are wide.

Prasugrel and Cancer

Prasugrel has two large CV outcome trials potentially providing additional data regarding its association with solid cancers: TRITON and TRILOGY. I summarize relevant features of them in Table 5 compared to the prasugrel part of DAPT.

Table 5: Prasugrel Outcome Trials

Trial	TRITON	TRILOGY	DAPT-P
Dates randomized	11/04-01/07	01/09-9/11	08/09-04/14
Population	ACS invasive	ACS medical	stents
N	13,608	9,456	3,686
Age, average y	61	66	59
Male	74%	61%	77%
Follow-up, average m	15	17	~20
Prasugrel discontinuation	18%	24%	~25%?
Complete follow-up	94%	79%	94%
Died	2.7%	8.9%	NA
Major/GUSTO bleed RR	1.4	1.3	1.7*
95% CI	1.1-1.7	0.9-1.9	NA
Solid cancer RR	1.5	0.9	1.3
95% CI	1.1-2.0	0.6-1.3	0.7-2.2
Solid ca/100 PEY (control)	1.0	1.0	NA
Non-CV death RR	1.2	1.0	1.2

95% CI	0.8-1.8	0.7-1.4	0.5-2.5
Died with solid ca RR	1.7	0.7	NA
95% CI	0.9-3.2	0.4-1.3	NA
Died %, solid ca pts (control)	22%	46%	NA

*GUSTO bleed RR DES subgroup; NA = not available currently to FDA; PEY = person exposure year; RR = risk ratio prasugrel/clopidogrel; CI = confidence interval

*COMMENT: What appears striking to me in Table 5 is the similarity in the bleeding, cancer, and non-CV death findings between TRITON and DAPT-P. All three adverse events are increased in the prasugrel arms of both studies with not too dissimilar point estimates and overlapping confidence intervals. TRILOGY appears to be the odd study out with dissimilar results, although its confidence intervals are still overlapping. I believe that the difference in TRILOGY may be the result of conduct issues, e.g., incomplete follow-up, that I document below. Another possibility is the differing results for studies in patients managed invasively compared to studies in patients managed medically. I discuss the latter in the **Anticoagulant Drugs and Cancer** section below.*

I have reviewed cancer findings from TRITON in my review from 2009 (Marciniak 2009) and from TRILOGY in my review from 2013. (Marciniak 2013) I summarize the most relevant findings from those reviews below.

TRITON

TRITON was a trial in ACS patients managed invasively of prasugrel vs. clopidogrel. TRITON is my index study for my concerns about CV drugs increasing cancer risk. I analyzed solid cancer rates in TRITON because my interpretation of the prasugrel 24-month mouse carcinogenicity study was that prasugrel may be a tumor promoter for a wide variety of solid cancers (excluding skin cancers.)

COMMENT: While the preclinical carcinogenicity studies have been interpreted as negative by the usual criteria, the sizing of the studies is inadequate for statistical confirmation of modest cancer promotion effects. Furthermore, the usual criteria (analyzing tumor incidences by site and sex) are inappropriate for analyzing an effect upon a wide range of solid tumors. My analyses of the prasugrel carcinogenicity studies did not follow the usual criteria but analyzed groups of solid cancers and suggested that prasugrel was promoting the growth of many solid cancers. Please see my 2009 review for the details (Marciniak 2009) but I have included my conclusions below:

> *"Because of the highly significant difference in hepatic adenomas, the moderately suggestive trend in hepatic cancers, the weakly suggestive trends in intestinal and lung cancers, the supportive data of the altered cell foci, and the absence of any tumors showing a clear reverse trend, I would still interpret the mouse study as suggestive of a carcinogenic effect of prasugrel in one species."*

Regardless, negative preclinical carcinogenicity studies do not rule out a drug being a cancer promoter in humans. The TSI memo's author has made this mistake previously: She rejected the possibility that ARBs are associated with increased rates of lung cancer in her memo dated 15 April 2013 (Southworth, Stockbridge et al. 2013) because "there is no evidence from nonclinical

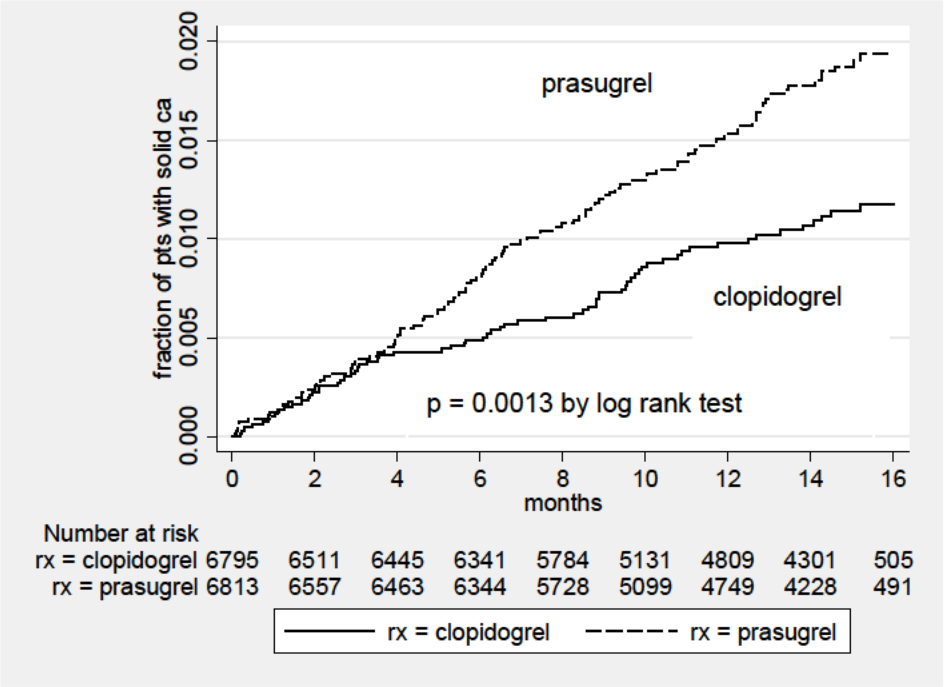
assessments of any of the ARBs that they are carcinogenic" and "we know of no case of specific lung-cancer promotion or true carcinogenesis for an orally administered agent" and concluding that "We regard it as implausible that ARBs somehow cause or accelerate cancer without a reasonable precedent or proposed mechanism . . ." Orally administered beta carotene is a recognized risk factor for lung cancer per the National Cancer Institute. (NCI 2012) The NCI bases its conclusion on the results of two large randomized controlled trials that document beta carotene as a risk factor or cancer promoter for lung cancer in humans, particularly smokers. (ATBCCP_Study_Group 1994; Omenn, Goodman et al. 1996) Beta carotene appears to be a cancer promoter despite negative carcinogenicity studies (Heywood, Palmer et al. 1985) and preclinical and epidemiologic evidence suggesting that beta carotene may prevent cancer. (Peto, Doll et al. 1981)

I have proposed a mechanism for how drugs that increase bleeding may increase solid cancer rates: Solid cancers are dependent upon neovascularization for their growth. If one of the body's defense mechanism is clotting to inhibit the neovascularization and the tumor growth, then drugs inhibiting clotting may promote solid cancer growth. That the coagulation system plays a role in malignancy is demonstrated by the well established observation that malignancy is frequently associated with a hypercoagulable state. (De Cicco 2004) While one hypothesis has been that the malignancy is inducing the hypercoagulable and there is evidence supporting that hypothesis, I advocate that the hypothesis that the coagulation system is also a defense mechanism against solid cancers should be explored.

There is another possible mechanism for how antiplatelet drugs may increase solid cancer rates: It is well established that platelets function in immunity as well as coagulation. (Morrell, Aggrey et al. 2014) While the immune functions of platelets have been studied predominantly regarding body defenses against microorganisms, I believe that the possibility that platelets play a role in immune defense against solid cancers should also be explored. It is also well established that many carcinogenic drugs impair immune surveillance. (Rubin 1964) Hence antiplatelet drugs such as clopidogrel and prasugrel impairing platelet-mediated cell immunity and promoting cancer growth is a possibility. This mechanism may not be shared with other drugs increasing bleeding, the oral anticoagulants, and could be platelet receptor specific. Because anticoagulants also appear to be associated with increased solid cancer rates, I judge that the data support better the coagulation defense mechanism than an immune surveillance mechanism.

The solid cancer (excluding non-melanoma skin and brain) event rates by arm in TRITON showed the strikingly different incidence curves shown in Figure 7.

Figure 7: Solid Cancer Event Incidence in TRITON



The solid cancer rates[3] begin to diverge at about 4 months and continue to diverge throughout 16-months of follow-up. The hazard ratio estimated by Cox regression is about 1.6 (95% CI 1.2-2.2). The absolute risk difference at 16 months is about 0.8%. Figure 7 includes recurrent cancers as well as new cancers, the results limited to new solid cancers are similar although of lower statistical significance (p = 0.024). I show the sites of the solid cancers in TRITON in Table 6.

Table 6: Solid Cancer Sites in TRITON

	clopidogrel	prasugrel
bladder	10	8
breast	1	6
carcinoid	1	0
cervix	1	1
colon	8	18

[3] In this document I refer to "cancer rates" and "cancers" for brevity. However, unless I specifically comment otherwise, the rates are fractions of patients with at least one cancer adverse event during the ITT trial period rather than rates or incidence of newly diagnosed cancers. Clinical trials do not always capture complete histories of cancers, so in some cases we cannot determine whether a cancer event is a newly diagnosed cancer or a recurrence. Regardless, because most cancer deaths result from the progression or recurrence of the cancer rather than the primary tumor, I recommend analyzing cancer events regardless of novelty. In CV trials the vast majority of first cancer events are newly diagnosed cancers and multiple cancers in one patient are uncommon. For this review I based site-specific cancer rates on the tabulations of first solid cancers and did not add in second cancers, if any.

	clopidogrel	prasugrel
esophagus	2	5
gi other	1	0
head & neck	2	1
kidney	2	3
liver	0	2
lung	14	19
melanoma	2	3
mesothelioma	0	1
other	1	0
pancreas	3	2
prostate	10	17
sarcoma	0	2
stomach	8	8
thyroid	1	0
unknown	1	7
uterus	1	0
total	69	103

The sites with higher rates in the prasugrel arm are mainly the more common sites, i.e., breast, colon, lung, and prostate. Unknown primaries (frequently lung or GI) also had a higher rate with prasugrel. Esophagus, a site perhaps detected because of bleeding, also had a higher rate although stomach and bladder, other sites detected because of bleeding, were balanced between the two arms.

COMMENT: I believe that the cancer results in TRITON are very well validated. They have been scrutinized both internally within the FDA and with the sponsor. The disagreements have predominantly been regarding whether to include other neoplasms such as skin cancers, whether to count both new and recurrent disease, and whether the differences represent a cancer promotion or early detection effect rather than regarding the identities of the solid cancers. I have detailed my reasons for excluding skin cancers, and brain tumors and hematologic malignancies, in my review and summarize them in the ***DAPT Study Results*** *section.*

DAPT provides additional evidence that the increase in solid cancer rates in TRITON are not the result of early detection in patients who bled. While I have argued that the continued divergence of the curves in Figure 7 and the similar survival rates after a solid cancer event for prasugrel and clopidogrel suggest tumor promotion rather than early detection, the facts that in DAPT the solid cancer increases occurred despite the 1-year run-in period and that mortality was increased due to the solid cancer increases provide compelling support for cancer promotion.

The solid cancer results in TRITON are solid: They support a statistically (p = 0.0013) and clinically (HR 1.6, absolute risk difference 0.8% at 16 months) significant increase in solid cancers with prasugrel vs. clopidogrel when prasugrel is dosed per the TRITON protocol.

Mortality rates after a solid cancer event in TRITON were high and similar in both arms, about 30% at 9 months. Because assigning a single cause of death (other than the cancer) is problematic in cancer patients and because the mortality rate following a solid cancer event is substantially higher than the late mortality rate in ACS patients without cancer, I analyzed deaths in cancer patients rather than deaths attributed to cancer (and I recommend primarily analyzing deaths in cancer patients rather than deaths attributed to cancer or non-CV deaths in all studies.) I show in Table 7 the numbers of cancer patients who died in TRITON.

Table 7: Deaths in Cancer Patients in TRITON

	Through end of study			With additional follow-up	
	Clopidogrel	Prasugrel	RR†	Clopidogrel	Prasugrel
New solid cancers*	14	22	1.6	22	36
Treatment emergent solid cancer* AEs	15	26	1.7	24	42
New malignancies	14	23	1.6	24	37
Treatment emergent malignancy AEs	16	27	1.7	28	43

*excluding non-melanoma skin and brain; †RR = risk ratio prasugrel/clopidogrel

The sponsor for TRITON acquired additional follow-up on the cancer patients. Regardless of whether one ignores or counts this additional follow-up, the relative risk of dying with cancer was about 1.5-1.7 fold higher in the prasugrel arm than in the clopidogrel arm.

All cause mortality was virtually identical in the two arms at the end of TRITON. However, because there was an early mortality benefit with prasugrel particularly in the STEMI substudy, mortality at the end of TRITON was trending unfavorably for prasugrel. I show the incidence curves for all cause mortality in Figure 8 and for non-CV mortality in Figure 9.

Figure 8: All Cause Mortality Incidence in TRITON

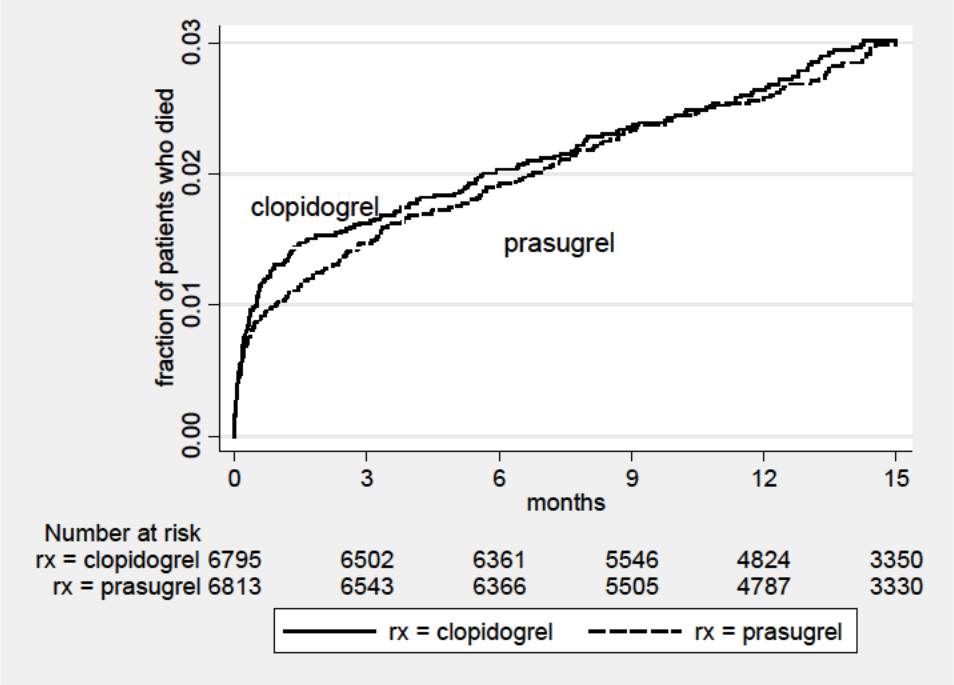
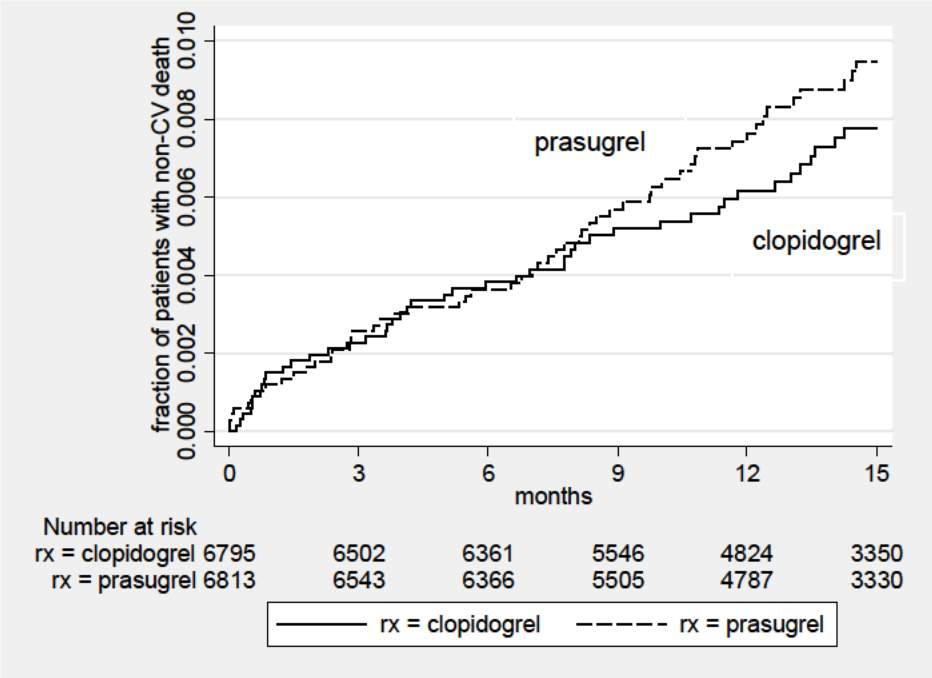


Figure 9: Non-CV Mortality Incidence in TRITON



While the separation of the non-CV death curves is not statistically significant by usual tests, the separation at about 9 months is striking and consistent with the increased cancer rates in the prasugrel arm.

COMMENT: In TRITON prasugrel produced about a 30% higher rate of major or minor TIMI bleeding than clopidogrel. The TRITON results are consistent with DAPT overall results in that the arms with greater platelet inhibition and more bleeding led to higher rates of solid cancers and solid cancer deaths and non-CV mortality. DAPT looks like an extension of TRITON.

As I discuss in the **Summary** section above, the antiplatelet drug trials in patients with substantial management by an invasive approach appear to show an association between bleeding and solid cancers while the non-invasive trials do not. We need to consider possible mechanistic differences between the two types of trials. One possibility is the use of drug eluting stents (DES) in the invasive trials. TRITON had substantial use of both types of stents, with about 47% of patients receiving at least one DES at the index PCI. There is no interaction between prasugrel and DES use in TRITON for solid cancers (RR for interaction term 1.0, $p > 0.8$) or for the primary MACE endpoint, for deaths, or for CV deaths. The simplest Cox regression model of non-CV mortality including only prasugrel, DES, and their interaction has hazard ratios (HRs) of about 2 for both prasugrel and DES use and an HR for the interaction of 0.35, with all terms significant (p's ≈ 0.015). However, in more comprehensive Cox models the interaction is not significant. I show one such model in Table 8.

Table 8: Cox Regression of Non-CV Mortality in TRITON

```
Cox regression -- Breslow method for ties

No. of subjects =        13608                     Number of obs   =     13608
No. of failures =           99
Time at risk    =  174264.8667
                                                   LR chi2(7)      =     84.92
Log likelihood  =   -883.98458                     Prob > chi2     =    0.0000

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         age |   1.083262   .0108698     7.97   0.000     1.062166    1.104777
        male |   1.421757   .3313628     1.51   0.131     .9004082    2.244974
    prasugrel |   1.883072   1.112817     1.07   0.284     .5913464    5.996416
         des |   1.110573   .5305733     0.22   0.826     .4353993    2.832738
des#prasugrel |   .3822446   .2405797    -1.53   0.127     .1113285     1.31243
         bms |    .392559   .1950346    -1.88   0.060      .148253    1.039456
bms#prasugrel |   1.220962   .7806721     0.31   0.755     .3486999    4.275163
------------------------------------------------------------------------------
```

While both prasugrel use and DES use alone were associated with higher non-CV mortality, patients receiving prasugrel with a DES experienced lower non-CV mortality. The prasugrel-DES interaction for deaths in solid cancer patients is similar.

COMMENT: The TRITON data do not strongly support a prasugrel-DES interaction and the observed interaction is in the wrong direction for explaining why the invasive trials appear to show an association between bleeding and solid cancers while the noninvasive trials don't. I suspect the borderline interaction is a chance variation. However, I do think we should examine other trials including DES for effects upon cancer and other disorders, e.g., infections.

TRILOGY

TRILOGY was a failed trial of prasugrel vs. clopidogrel in ACS patients managed medically (as opposed to the TRITON invasively managed ACS patients.) It failed to demonstrate superiority of prasugrel to clopidogrel regarding its primary endpoint of reducing CV death, MI, and stroke in such patients.

Because of the prasugrel cancer results, I had recommended that the sponsor examine cancer rates in an adequately sized study to have 90% power of detecting a 50% increase in the rate of development of new solid cancers. For cancer rates similar to those in TRITON, i.e., a control rate of about 1% per year, the number of events needed is about 279. A large trial is needed, e.g. a 22,000 patient trial with mean follow-up of a year and minimum follow-up exceeding 8 months is an example.

We (the FDA) did not require an adequately sized study but recommended that the sponsor capture cancer events in TRILOGY. Despite this recommendation, cancer event capture appears to have been problematic in TRILOGY. I summarize below the many problems with TRILOGY:

- TRILOGY was underpowered for cancer analyses. Rather than the 279 new solid cancers needed for adequate power, it reported 138 new solid cancers, 147 solid cancers including recurrent. TRILOGY was half the size needed.

- Study drug discontinuation rates were high. Per the NEJM article 24% of prasugrel and 22% of clopidogrel patients discontinued study drug during the study period. Working from the exrxendt ("Exposure Prescribed End Date ") variable in the NDA submission, I calculated that about 30% of patients had discontinued study drug more than 30 days prior to death or study end. By 120 days (the time at which the cancer rates started to diverge in TRITON) about 15% of prasugrel patients had already discontinued study drug. Study drug discontinuations are particularly problematic in TRILOGY because of the protocol specification regarding adverse event (AE) reporting—see next bullet.

- The protocol specified collecting adverse events only until 30 days after the last dose of study drug unless the investigator "feels the events were related to either study drug or a protocol procedure." While the protocol does state that cancers should be reported through study end, cancer events were adverse events. The statistics on cancer rates that I present below suggest that cancer events were underreported.

- Follow-up was incomplete. The NEJM article reported that about 6% of patients did not complete the study. However, from the data sets submitted to the NDA I can verify only that about 80% of the patients died or had a last contact on or after the study end date (or maximum treatment duration) and only about 70% of patients died or had a visit with vital signs on or after the end date.

- Solid cancer rates were low in TRILOGY. In TRILOGY the solid cancer rate was about 0.92 per 100 person exposure years (PEY) while in TRITON it was about 1.28 per 100 PEY (for both arms combined). Yet TRILOGY had a higher median age (66) than TRITON (61) and age is one of the most predictive risk factors for cancer rates. However, the differences in overall solid cancer rates are not as prominent as the differences in cancer rates in some geographic regions—see next bullet.

- Asian and Eastern European sites appear to have underreported cancers in TRILOGY. About 21% of randomized patients were from Asia in TRILOGY while none were from Asia (excluding Israel) in TRITON. Reported solid cancer rates in Asian patients in TRILOGY were very low, about 0.15 per 100 PEY, or more than 10-fold lower than in the US (1.7) and Western Europe (2.0). Cancer rates in Asia as reported in international statistics are 2 to 3 fold lower in Asia than in the Western world. Cancer rates in Asia in the apixaban ARISTOTLE trial were about half of Western rates. Ten-fold lower suggests underreporting. About 35% of randomized patients were from Eastern Europe in TRILOGY while 24% were from Eastern Europe in TRITON. Reported solid cancer rates in Eastern European patients in TRILOGY were low, about 0.68 per 100 PEY compared to 1.14 in TRITON and 1.17 in ARISTOTLE. Hence there also appears to be underreporting of solid cancers from Eastern Europe in TRILOGY.

- Cancer results were only favorable in the second half of the trial. The solid cancer results were unfavorable for prasugrel in patients enrolled in the first half of the trial (RR about 1.07) becoming favorable in patients enrolled in the second half (RR about 0.7) as shown in Table 9.

Table 9: Solid Cancer rates for Patients Enrolled by Half in TRILOGY

	half 1		half 2	
	rate*	RR†	rate*	RR†
clopidogrel	0.93		0.99	
prasugrel	0.99	1.07	0.69	0.70

*rate per 100 PEY; †RR = risk ratio prasugrel/clopidogrel

The interaction between treatment and trial half for the solid cancer rates as reported by the sponsor is statistically significant (p = 0.033 by Cox regression). The rates above are also consistent by quarter: clopidogrel is favorable in quarters 1 and 2 patients and prasugrel in quarters 3 and 4 patients. The anomalous rate appears to be the low prasugrel rate in the second half patients.

Ignoring the limitations of the problems described above, the sponsor analyzed "all new non-benign neoplasms" and calculated a hazard ratio (HR) of 1.045 (95% confidence interval (CI) 0.767-1.425, p = 0.786.) I analyzed solid cancer events and calculated a HR of 0.96 (95% CI 0.68-1.36, p = 0.82.)

COMMENT: TRITON and TRILOGY are not absolutely inconsistent because the confidence intervals for their cancer rates overlap, but TRILOGY has been interpreted as establishing that prasugrel does not have a cancer risk. Because of the many problems with TRILOGY I judge its results to be unreliable. I believe that the DAPT results, which are more consistent with TRITON than with TRILOGY, now confirm that TRITON provides the better estimate of cancer risk and that prasugrel does increase the risk of solid cancers. DAPT also confirms that the increased risk of solid cancers with prasugrel is likely a cancer promoter effect and not a detection bias because the difference in cancer rates was manifested during the thienopyridine withdrawal period long (> 1 year) after the initiation of thienopyridine treatment.

The TRITON-TRILOGY-DAPT comparisons also confirm my belief that a confirmatory trial, one allegedly with specific directions for ascertaining the event of interest, is not necessarily more reliable than the index trial lacking pre-specifications. I believe that TRILOGY demonstrates that, by sloppy conduct, one may obscure a signal despite having a goal to clarify whether that signal exists. The TRITON-TRILOGY-DAPT comparisons have implications for our recommendations regarding how trials must be conducted to maximize confidence in their results. However, while it is clear that TRILOGY had conduct issues, it is not clear that the TRILOGY results are completely wrong. The vorapaxar TRACER-TRA2P comparison is similar to the prasugrel TRITON-TRILOGY comparison as I discuss in the ***Other Antiplatelet Drugs and Cancer*** *section below.*

Clopidogrel and Cancer

Clopidogrel has been studied in a heterogeneous set of outcome trials, many performed long ago. I show the features of the older clopidogrel trials for which we have datasets in Table 10 and the newer trials (including an NIH trial SPS3 for which we do not have datasets) in Table 11.

Table 10: Older Clopidogrel Outcome Trials

Trial	CAPRIE	CURE	CREDO	CHARISMA
Dates randomized	03/92-02/95	12/98-09/00	06/99-04/01	10/02-11/03
Population	high risk	ACS	PCI	high risk
N	19,185	12,562	2,116	15,603
Age,average y	63	65	62	64
Male	72%	62%	71%	70%
Control	ASA	placebo	clopidogrel 28d	placebo
ASA - clopidogrel	0	75-325 mean 170-150	325 28d then 81-325	75-162
ASA - control	325			
Follow-up, average m	23	10	12	28
Clopidogrel discontinued	24%	20%	37%	20%
Complete follow-up	87%	77%	91%	86%
Died	5.9%	6.0%	2.0%	4.8%
Major/severe bleed RR	0.9	1.4	1.3	1.25
95% CI	NA	1.1-1.7	1.0-1.8	1.0-1.6
Solid cancer RR	1.0	1.0	1.4	0.9
95% CI	0.8-1.2	0.7-1.5	0.7-2.7	0.8-1.1
Solid ca/100 PEY (control)	1.4	1.0	1.4	1.0
Non-CV death RR	1.0	1.1	0.6	1.0
95% CI	0.8-1.3	0.7-1.6	0.2-2.0	0.8-1.2
Died with solid ca RR	1.1	0.8	3	0.8
95% CI	0.8-1.5	0.4-1.6	0.3-29	0.6-1.1
Died %, solid ca pts (control)	33%	39%	7%	34%

NA = not available currently to FDA; PEY = person exposure year; RR = risk ratio clopidogrel/control; CI = confidence interval

Table 11: Newer Clopidogrel Outcome Trials

Trial	ACTIVE-W	ACTIVE-A	PRoFESS	SPS3	DAPT-C
Dates randomized	06/03-12/04	06/03-05/06	09/03-07/06	03-11	08/09-04/14
Population	afib	afib	hx of stroke	recent stroke	stents
N	6,706	7,554	20,332	3,020	7,962
Age, average y	71	72	66	63	63
Male	66%	58%	64%	63%	74%

Trial	ACTIVE-W	ACTIVE-A	PRoFESS	SPS3	DAPT-C
Control	warfarin	placebo	ASA+ dipyridamole	placebo	placebo
ASA - clopidogrel	75-100	75-100	1st 2027	325	75-325 6m 75-162 >6m
ASA - control	12%		50		
Follow-up, average m	15	43	30	41	~20
Clopidogrel discontinued	14% @ 18m	16% @ 1y 39% @ 4y	23%	30%	~25%?
Complete follow-up	94%	82%	96%	87%	94%
Died	4.7%	21.8%	7.1%	6%	NA
Major/severe bleed RR	1.1	1.6	0.9	2.0	1.6
95% CI	0.8-1.5	1.3-1.9	0.8-1.0	1.4-2.7	NA
Solid cancer RR	0.9	1.1	1.0	NA	1.2
95% CI	0.7-1.2	0.9-1.3	0.9-1.2	NA	0.8-1.7
Solid ca/100 PEY (control)	2.2	1.6	1.2	NA	NA
Non-CV death RR	0.7	0.9	1.0	1.3	1.9
95% CI	0.5-1.1	0.8-1.1	0.8-1.2	0.8-2.1	1.1-3.1
Died with solid ca RR	0.7	1.0	1.1	NA	NA
95% CI	0.4-1.3	0.8-1.3	0.9-1.4	NA	NA
Died %, solid ca pts (control)	28%	56%	45%	NA	NA

NA = not available currently to FDA; PEY = person exposure year; RR = risk ratio clopidogrel/control; CI = confidence interval

I did not include COMMIT and CLARITY in the tables because of their short follow-up durations, too short to be informative regarding cancer development. As can be judged from the tables, the trials are heterogeneous regarding years conducted, populations studied, ages, the use of aspirin, control, clopidogrel discontinuation rates, duration of follow-up, completeness of follow-up, and results.

COMMENT: Of the nine trials, only CREDO and DAPT-C have a signal for higher solid cancer rates with clopidogrel (but we don't have cancer data for SPS3) while only SPS3 and DAPT have a signal for increased non-CV death rates with clopidogrel. However, most of the trials have significant limitations that I discuss below.

CAPRIE

CAPRIE was a trial in high CV risk patients of clopidogrel vs. aspirin 325 mg. CAPRIE was neutral for bleeding, solid cancers and non-CV deaths. Because bleeding was about the same in the two arms, I consider the results to be consistent. The completeness of follow-up was not good and incomplete follow-up appears to be a limitation of many of the trials (with the exception of the early-terminated ACTIVE-W trial) conducted by the clopidogrel innovator.

CAPRIE also illustrates what may be the most serious limitation of cancer ascertainment in some CV trials: In CAPRIE "Adverse experiences of patients were recorded for the duration of their

follow-up, except in those patients who permanently discontinued study drug early; for these patients adverse experiences were counted up to 28 days after discontinuation." Yet we might expect a patient to develop an initial, vague symptom of cancer and discontinue study drug, but not be diagnosed until weeks later. In CAPRIE 24% of patients discontinued clopidogrel prematurely so we may be missing many cancers.

CURE

CURE was a trial in ACS patients of clopidogrel vs. placebo with background aspirin. About 18% of the patients underwent PCI or CABG. CURE showed neutral solid cancer and non-CV death results despite a substantially higher rate of bleeding in the clopidogrel arm. However, treatment duration could be as short as 3 months, the median follow-up duration was too short (10 months) and the completeness of follow-up too low (77%) to have any confidence that the results are accurate and complete.

CREDO

CREDO was a factorial trial in PCI patients of a pre-procedural clopidogrel loading dosing vs. none and then 3 vs. 12 months of clopidogrel. I doubt that the loading dose is relevant to cancer rates so I do not analyze that randomized comparison in this review. The CREDO 3 vs. 12 months comparison does appear to support the hypothesis that higher bleeding rates are associated with higher solid cancer rates, although the difference in solid cancer rates is not even nominally statistically significant. The low point estimate for the non-CV death RR (0.6) is not inconsistent because there were few non-CV deaths in CREDO (4 vs. 7) so the confidence interval is wide. Lung cancers were 5 clopidogrel vs. 0 control, nominally statistically significant, but not greatly concerning given the small number. CREDO was a relatively small, shorter duration trial that started with clopidogrel use in both arms for the first 28 days. While I believe it supports the hypothesis, the support by the study alone is weak.

CHARISMA

CHARISMA was a trial in high CV risk patients of clopidogrel vs. placebo against a background of aspirin. CHARISMA was similar to CAPRIE except that, because clopidogrel was added to aspirin rather than aspirin serving as the control, bleeding rates were higher in the clopidogrel arm. Despite that, solid cancer and non-CV death rates were similar. Like CAPRIE, the completeness of follow-up was not good. Also like CAPRIE, CHARISMA had a limitation regarding reporting adverse events (AEs): For CAPRIE, AEs were not to be reported >28d after drug discontinuation while for CHARISMA treatment-emergent AEs were defined as occurring on-treatment or within 28d of treatment discontinuation. The solid cancer rates in CHARISMA per 100 PEY were lower in CHARISMA than in comparable trials, suggesting underreporting in CHARISMA, although cross-trial comparisons are not reliable. Within these limitations CHARISMA is suggestive that clopidogrel does not increase solid cancer or non-CV death rates.

ACTIVE-W

ACTIVE-W was one of the trials of the ACTIVE program in atrial fibrillation (afib) patients. ACTIVE-W randomized afib patients to clopidogrel+aspirin vs. warfarin. (ACTIVE patients could also be randomized to irbesartan vs. placebo in a factorial design, but I do not discuss the

irbesartan findings here. Please see my review of angiotensin receptor blockers and cancer.) ACTIVE-W had a small difference in bleeding and solid cancer rates between its clopidogrel+aspirin arm and its warfarin arm. There were more lung cancers (21:13) and prostate cancers (19:13) in the warfarin arm. While the non-CV death difference appears favorable to clopidogrel, there was no difference in all-cause mortality. ACTIVE-W supports little difference in bleeding associated with little difference in solid cancer rates.

ACTIVE-A

ACTIVE-A randomized afib patients intolerant of warfarin to clopidogrel vs. placebo with a background of aspirin. ACTIVE-A results are a variation on CHARISMA: The major bleed RR in ACTIVE-A was higher than that in CHARISMA and in ACTIVE-A, unlike CHARISMA, there is a hint of a higher solid cancer rate. Bladder, esophagus and stomach, and prostate cancer rates were substantially higher in the clopidogrel arm. The non-CV death rates in ACTIVE-A were not differentiated. Completeness of follow-up was not high. ACTIVE-A results don't rule out an effect of clopidogrel on solid cancer rates but neither are they suggestive of one.

PRoFESS

PRoFESS was another factorial trial. PRoFESS randomized patients with a history of ischemic stroke randomizing to clopidogrel vs. aspirin plus dipyridamole and telmisartan vs. placebo. I do not discuss the telmisartan randomized comparison here. PRoFESS was neutral for bleeding, solid cancer, and non-CV death rates. Discontinuation of clopidogrel was high, follow-up completeness was not great, and only serious AEs were captured. PRoFESS supports no difference in bleeding associated with no difference in solid cancers..

SPS3

SPS3 was an NIH-sponsored trial of clopidogrel and aspirin vs. aspirin alone in recent stroke. We do not have data sets or a detailed study report with cancer data for it. I abstracted its information from its publication. Noteworthy is that the clopidogrel arm had about a 2-fold higher "major hemorrhage" and a higher non-CVD death rate, the latter not attributed to bleeding deaths. While the non-CV death difference is not statistically significant, the difference in all cause mortality is (hazard ratio 1.5, $p = 0.004$). We do not currently have cancer statistics for SPS3. However, per its protocol SPS3 only required "scrupulous standardized documentation" for "nine categories of events", i.e., ones believed to be related to antiplatelet drugs and not including cancer. SPS3 may not have complete cancer ascertainment. SPS3 is another trial that suggests that clopidogrel is associated with higher bleeding rates and higher non-CV mortality.

SUMMARY COMMENT FOR CLOPIDOGREL TRIALS: Considering the results of the older clopidogrel trials at face value, it is not surprising why I concluded in 2009 that those trials suggested that clopidogrel is not associated with an increased risk of solid cancers. The later trials, with the possible exception of SPS3, also do not suggest a risk. Currently we do not have the cancer data for SPS3—and what was collected regarding events may not be adequate for ascertaining cancer rates accurately—but its non-CV mortality results are concerning.

One possibility for the neutral results in the vast majority of the clopidogrel trials may be incomplete follow-up and cancer ascertainment. While I have summarized above the statistics

*suggesting the problems with incomplete follow-up, I do not know of any way of verifying that cancer ascertainment was incomplete. I discussed in the **Summary** section above one adverse event collection limitation of two of the trials, CAPRIE and CHARISMA.*

*There is another possibility for the neutral results: Solid cancer rates have been differentiated predominantly in trials with an invasive management component, like DAPT. I discuss this possibility in the **Other Antiplatelet Drugs and Cancer** section below.*

Other Antiplatelet Drugs and Cancer

There are two other new antiplatelet drugs studied recently in large outcome trials: ticagrelor and vorapaxar. Ticagrelor is a reversible $P2Y_{12}$ receptor inhibitor. Vorapaxar (unlike clopidogrel, prasugrel, and ticagrelor) is an inhibitor of the PAR-1 receptor rather than the $P2Y_{12}$ receptor. Ticagrelor has one large, clopidogrel-controlled outcome trial (PLATO) and vorapaxar has two large, placebo-controlled outcome trials (TRACER and TRA2P.) I summarize relevant features of them in Table 12.

Table 12: Ticagrelor and Vorapaxar Outcome Trials

New antiplatelet drug	ticagrelor	vorapaxar	
Trial	PLATO	TRA2P	TRACER
Dates randomized	10/06-07/08	09/07-11/09	12/07-11/10
Population	ACS	High risk	ACS
N	18,624	26,449	12,944
Age, median y	62	61	64
Male	72%	76%	72%
PCI	55%	8%*	58%
Clopidogrel use	(control)	62%	92%
Aspirin use	97%	94%	99%
Follow-up, median m	10.5	30	16
Drug discontinuation	23%	24%	28%
Complete follow-up	86%	96%	94%
Died	4.8%	4.3%	4.8%
TIMI major bleed RR	1.0	1.5	1.5
95% CI	0.8-1.2	1.2-1.8	1.2-1.9
Solid cancer RR	0.9	1.0	1.4
95% CI	0.7-1.2	0.9-1.1	1.1-1.9
Solid ca/100 PEY (control)	1.5	1.4	1.0
Non-CV death RR	0.9	1.0	1.1
95% CI	0.6-1.2	0.8-1.2	0.8-1.4
Died with solid ca RR	0.7	1.0	1.5
95% CI	0.4-1.4	0.8-1.2	0.8-2.4
Died %, solid ca pts (control)	23%	30%	26%

PEY = person exposure year; RR = risk ratio new drug/control; CI = confidence interval

I comment on the trial results below.

PLATO

PLATO was a trial in both invasively and medically managed ACS patients of ticagrelor vs. clopidogrel. PLATO had serious conduct issues as I detailed in my review of it. It had a short median follow-up (10.5 months), a substantial (although not unusual) rate of drug discontinuation (23%), and incomplete follow-up (about 86% complete). It can be interpreted as consistent with the hypothesis that neutral bleeding is associated with neutral solid cancer rates because overall TIMI major bleeding was neutral as were solid cancer rates and non-CV death rates. While overall TIMI major bleeding was neutral, non-CABG-related TIMI major bleeding rate was higher in the ticagrelor arm (hazard ratio about 1.2), so one could argue that PLATO is not supportive. However, given the short duration and incompleteness of follow-up, I judge PLATO to be neutral or uninterpretable.

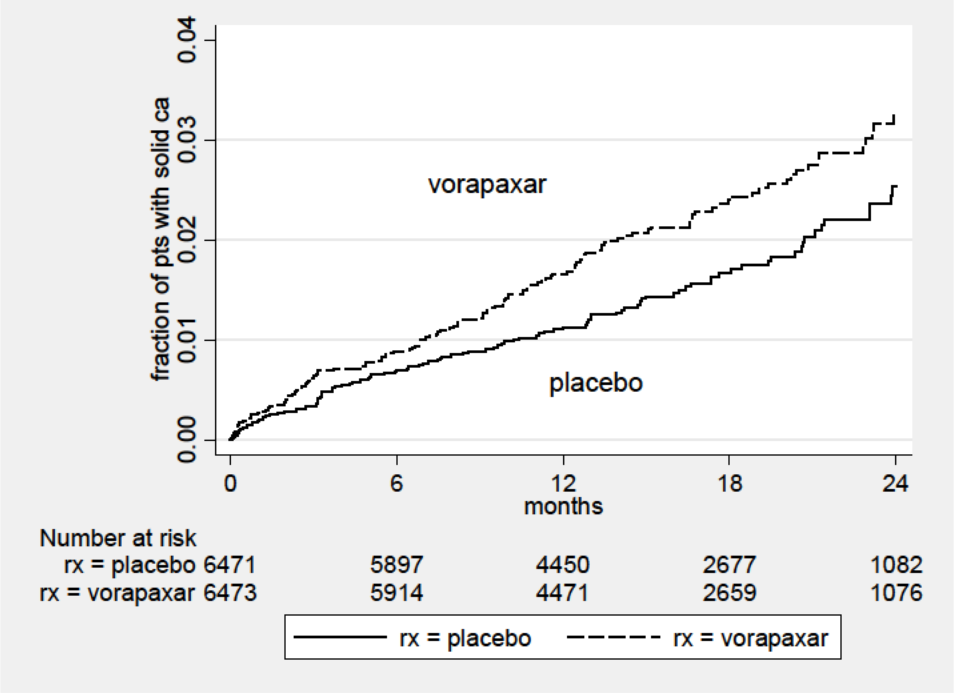
TRA2P

TRA2P was a trial in high CV risk patients of vorapaxar vs. placebo. TRA2P is the largest of the long term antiplatelet and anticoagulant drug trials. About 94% of patients received aspirin and 78% a thienopyridine, usually clopidogrel. It showed a moderately higher rate of TIMI major and other bleeding in the vorapaxar arm but solid cancer and non-CV mortality rates comparable to placebo. Its one identified design flaw is that the protocol specified phone contacts for patients who had discontinued treatment but stated that "During these telephone contacts, the investigator/qualified designee will also collect information about any serious adverse event that occurred up to 60 days after the last dose of study treatment." I discussed above regarding CAPRIE how such an instruction may hinder complete capture of cancer events. Within this limitation TRA2P does not support an association between bleeding and solid cancers but it is inconsistent with TRACER.

TRACER

TRACER was a study in ACS patients of vorapaxar added to standard therapy, usually aspirin (99%) and clopidogrel (92%). About 58% of patients underwent PCI and 10% CABG. About 31% of patients had a DES inserted. TRACER terminated early because of excessive bleeding without an offsetting benefit. TRACER showed significantly higher rates of bleeding and of solid cancer events in the vorapaxar arm (RR or hazard ratio for solid cancers 1.4, 95% CI 1.1 to 1.9, $p \approx 0.01$). Non-CV mortality was only slight higher in the vorapaxar arm (RR 1.1) while deaths in solid cancer patients were about 50% higher with vorapaxar but not statistically significantly increased. I show the incidence curves for solid cancer events in Figure 10.

Figure 10: Solid Cancer Event Incidence in TRACER



The solid cancer event incidence curves diverge early and then almost converge at 6 months, suggesting an early detection bias in the vorapaxar arm. They then continue to diverge for most of the study. The convergence near the end may reflect fewer numbers of patients at risk near the end and hence higher variability in the rate point estimates.

About 57% of TRACER patients had a PCI within 7 days and 31% of TRACER patients had a DES inserted early. Neither early invasive approach nor DES insertion are significant factors or interact with vorapaxar for solid cancer incidence.

The sites responsible for the divergence in the first 3 months were colon (12 vs. 3), lung (10 vs 6) and prostate (4 vs. 0). I show the incidence curves for colon cancer in Figure 11 and for lung cancer in Figure 12.

Figure 11: Colon Cancer Event Incidence in TRACER

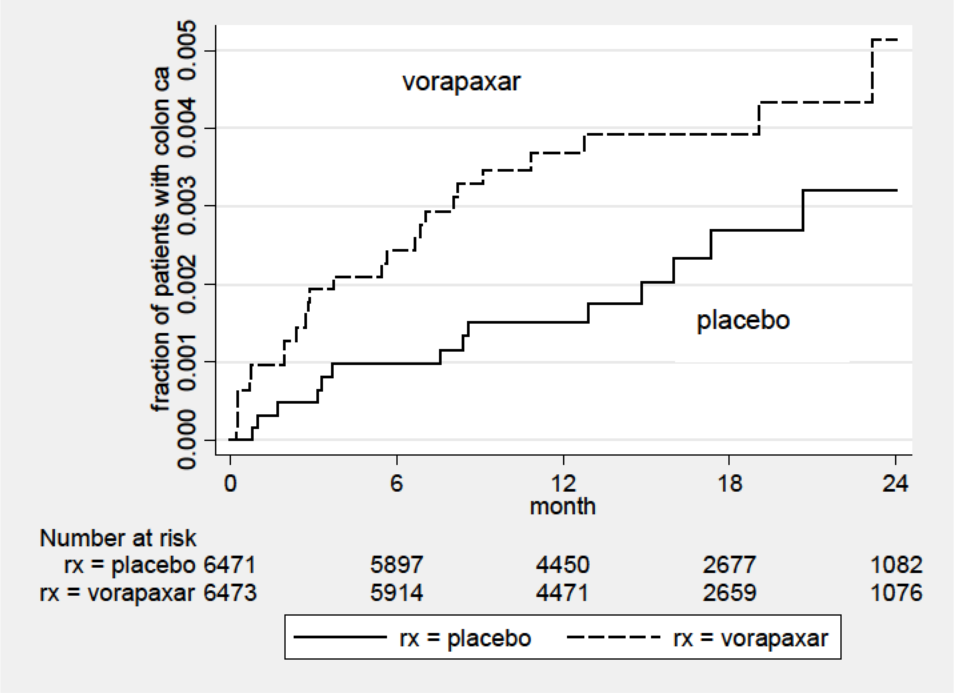
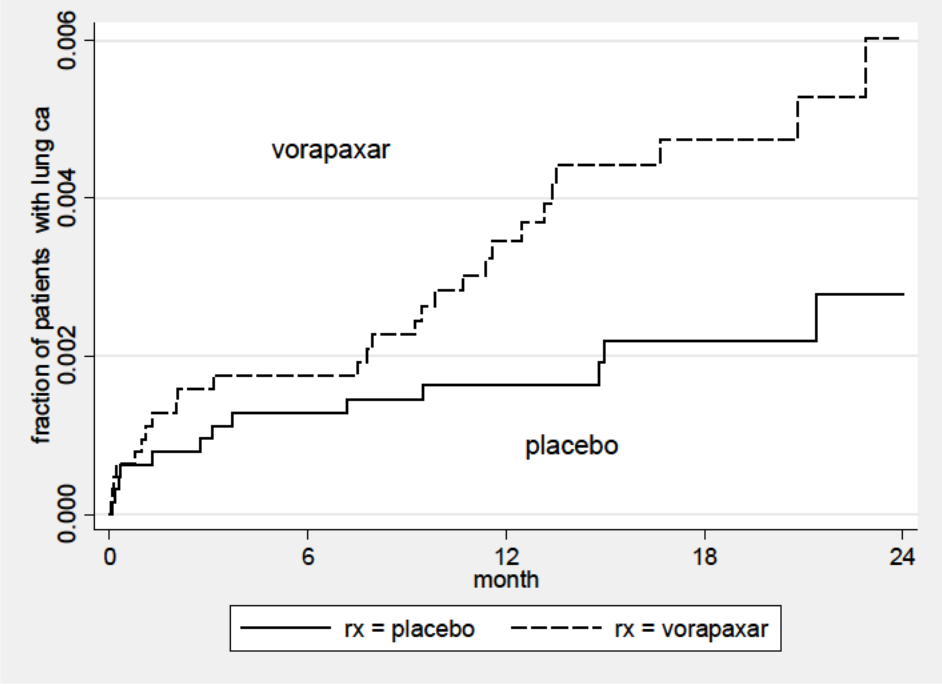


Figure 12: Lung Cancer Event Incidence in TRACER



The incidence curves for the two cancers differ: The colon cancer curves diverge immediately but then almost converge late (18-24m). The lung cancer curves both show an early steeper slope, vorapaxar greater than placebo, but then they diverge starting about 8 months and continue to diverge.

COMMENT: I interpret the colon cancer curves as suggesting an early detection bias for colon cancer in the vorapaxar arm because of higher bleeding. There appears to be catch-up later in the placebo arm. For lung cancer the early steeper slopes in both arms are likely due to detection during the x-rays and fluoroscopy performed during the index hospitalization. The later divergence may be due to cancer promotion with vorapaxar.

I show the sites of the solid cancers during the entire ITT period of TRACER in Table 13.

Table 13: Solid Cancer Sites in TRACER

	placebo	vorapaxar
bile duct	3	1
bladder	11	18
breast	3	4
colon	13	24
esophagus	3	3
head & neck	4	4
kidney	8	6
liver	2	1
lung	12	23
melanoma	6	9
other	1	0
ovary	3	1
pancreas	1	3
prostate	9	14
sarcoma	0	2
stomach	8	5
testes	1	0
thyroid	0	2
unknown	1	3
uterus	1	5
total	90	128

The sites with substantially higher rates in the vorapaxar arm are bladder, colon, lung, prostate, and uterus.

COMMENT: TRACER appears to show some evidence for a detection "bias", or earlier detection of cancers that bleed in the vorapaxar arm due to more bleeding with vorapaxar than with placebo. This bias likely is more prominent particularly for GI cancers with vorapaxar because vorapaxar is not a prodrug like clopidogrel and prasugrel and hence is active in the gut.

While this mechanism should also be operative for TRA2P, patient scrutiny during the initial hospitalization for ACS in TRACER was likely much higher than during the outpatient initiation of vorapaxar in TRA2P.

I am impressed by the similarities between the prasugrel trials and the vorapaxar trials: Both of the ACS, largely early invasive trials (TRITON and TRACER) showed statistically significant increases in solid cancers in the arms with more bleeding. And both of the noninvasive, predominantly medical management trials (TRILOGY and TRA2P) showed no differences in solid cancer rates. This distinction is also apparent for the clopidogrel trials, with the one invasive trial CREDO showing an effect upon cancer rates and the other noninvasive cardiac trials being negative. The cerebrovascular trial SPS3 may be the exception.

Because there appears to be an association between bleeding and cancer rates, a good question is whether anticoagulant drugs show this association like the antiplatelet drugs. Hence I compared cancer rates in all recent trials of new oral anticoagulant (NOAC) drugs. I present and discuss the results for the anticoagulants next.

Anticoagulant Drugs and Cancer

I show selected characteristics and results for the large outcome trials of NOACs in Table 14 and Table 15.

Table 14: New Oral Anticoagulant Outcome Trials 1

New oral anticoagulant	apixaban			rivaroxaban	
Trial	APPRAISE	ARISTOTLE	AVERROES	ATLAS	ROCKET
Dates randomized	03/09-11/10	12/06-02/10	09/07-12/09	11/08-01/11	12/06-06/09
Population	ACS	afib	afib	ACS	afib
N	7,392	18,201	5,598	15,526	14,264
Age, median y	67	70	70	61	73
Male	68%	65%	59%	75%	60%
Invasive	50%	NA	NA	60%	NA
Control	placebo	warfarin	aspirin	placebo	warfarin
Clopidogrel use	81%	2%	1%	93%	2.5%
Aspirin use	97%	31%	(control)	99%	36%
Follow-up, median m	8	21	13	14	22
New drug discontinuation	24%	25%	22%	28%	24%
Complete follow-up	98%	85%	86%	80%	78%
Died	4.3%	7.0%	4.7%	3.3%	8.6%
Major/severe bleed RR	2.6	0.6	1.1	2.3	1.0
95% CI	1.5-4.5	0.5-0.7	0.7-1.8	1.6-3.2	0.9-1.2
Solid cancer RR	2.5	0.9	0.9	1.2	1.1
95% CI	1.4-4.5	0.7-1.0	0.6-1.4	0.9-1.6	0.9-1.4
Solid ca/100 PEY (control)	0.6	1.7	1.5	0.8	1.5
Non-CV death RR	1.6	0.9	0.7	1.1	1.0

New oral anticoagulant	apixaban			rivaroxaban	
Trial	APPRAISE	ARISTOTLE	AVERROES	ATLAS	ROCKET
95% CI	0.9-2.9	0.8-1.1	0.5-1.0	0.6-1.8	0.8-1.2
Died with solid ca RR	2.2	0.8	0.5	0.9	1.2
95% CI	0.7-7	0.6-1.0	0.2-1.2	0.5-1.7	0.9-1.7
Died %, solid ca pts (control)	27%	31%	28%	30%	32%

PEY = person exposure year; RR = risk ratio new drug/control; CI = confidence interval

Table 15: New Oral Anticoagulant Outcome Trials 2

New oral anticoagulant	rivaroxaban	dabigatran	edoxaban	ximelagatran	
Trial	J-ROCKET	RELY	ENGAGE	SPORTIF III	SPORTIF V
Dates randomized	06/07-11/08	12/05-12/07	11/08-11/10	08/00-09/01	08/00-12/01
Population	afib	afib	afib	afib	afib
N	1,280	18,113	21,105	3,407	3,922
Age, median y	72	72	72	71	73
Male	80%	64%	62%	69%	69%
Invasive	NA	NA	NA	NA	NA
Control	warfarin	warfarin	warfarin	warfarin	warfarin
Clopidogrel use	NA	6%	2.3%	0%	o%
Aspirin use	38%	40%	30%	12%	18%
Follow-up, median m	19	24	34	15	20
New drug discontinuation	26%	24%	34%	18%	37%
Complete follow-up	90%	91%	90%	88%	83%
Died	1.8%	7.6%	10.8%	4.4%	6.1%
Major/severe bleed RR	0.9	0.9	0.7	0.7	0.7
95% CI	0.5-1.4	0.8-1.0	0.6-0.8	0.5-1.1	0.5-1.0
Solid cancer RR	0.9	1.1	1.0	1.0	0.8
95% CI	0.5-1.7	0.9-1.3	0.9-1.1	0.7-1.5	0.6-1.1
Solid ca/100 PEY (control)	1.9	2.1	1.7	1.8	2.7
Non-CV death RR	0.3	1.0	1.0	0.7	0.7
95% CI	0.1-1.4	0.8-1.2	0.9-1.2	0.4-1.3	0.5-1.1
Died with solid ca RR	1.0	0.9	1.1	1.3	0.7
95% CI	0.1-16	0.7-1.2	0.9-1.4	0.6-3.2	0.4-1.3
Died %, solid ca pts (control)	5%	32%	30%	21%	30%

PEY = person exposure year; RR = risk ratio new drug/control; CI = confidence interval

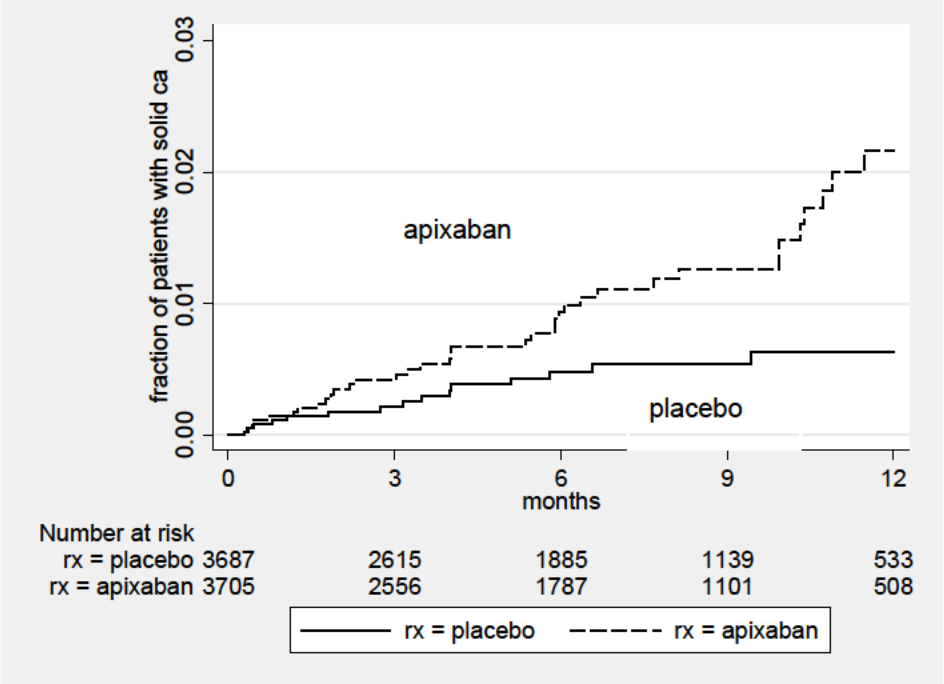
I provide additional data regarding the trials below.

APPRAISE

APPRAISE (APPRAISE-2) was a trial of apixaban vs. placebo on top of standard antiplatelet therapy in patients with a recent (within 7 days) ACS episode. APPRAISE terminated early because of an increase in bleeding with apixaban without an offsetting decrease in ischemic

events. Both bleeding and solid cancer rates were dramatically higher in the apixaban arm. I show the solid cancer event incidence in APPRAISE in Figure 13.

Figure 13: Solid Cancer Event Incidence in APPRAISE



The increased incidence of solid cancers with apixaban in APPRAISE was statistically significant: hazard ratio (HR) 2.5 (95% CI 1.4-4.6, p=0.002). Non-CV deaths were also more frequent (although not quite nominally statistically significantly) with apixaban: HR 1.6 (95% CI .94-2.9, p = 0.079). There were no interactions between apixaban use and invasive approach or DES use for either solid cancer incidence or non-CV mortality.

I show the sites of the solid cancer in APPRAISE in Table 16.

Table 16: Solid Cancer Sites in APPRAISE

	placebo	apixaban
anus	1	0
bile duct	0	1
bladder	0	5
breast	0	1
colon	5	4
esophagus	0	1
gi other	0	1
head & neck	1	0
kidney	0	2
lung	2	8
ovary	0	1

	placebo	apixaban
pancreas	1	3
prostate	2	1
stomach	2	6
testes	0	1
unknown	1	1
uterus	0	1
total	15	37

The cancer sites with higher incidence and higher rates in the apixaban arm were bladder, lung, and upper gastrointestinal (UGI – esophagus and stomach). Kidney and pancreas cancer sites were also more frequent with apixaban but few in number. The incidence curves for the higher incidence sites should be informative so I show bladder cancer incidence in Figure 14, lung cancer incidence in Figure 15, and upper GI cancer incidence in Figure 16.

Figure 14: Bladder Cancer Event Incidence in APPRAISE

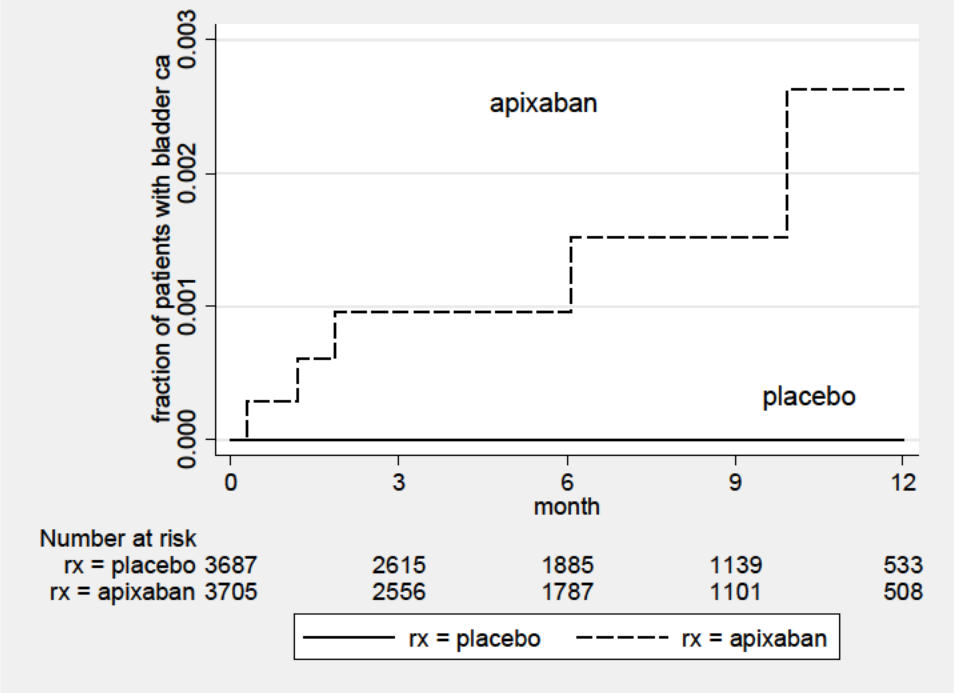


Figure 15: Lung Cancer Event Incidence in APPRAISE

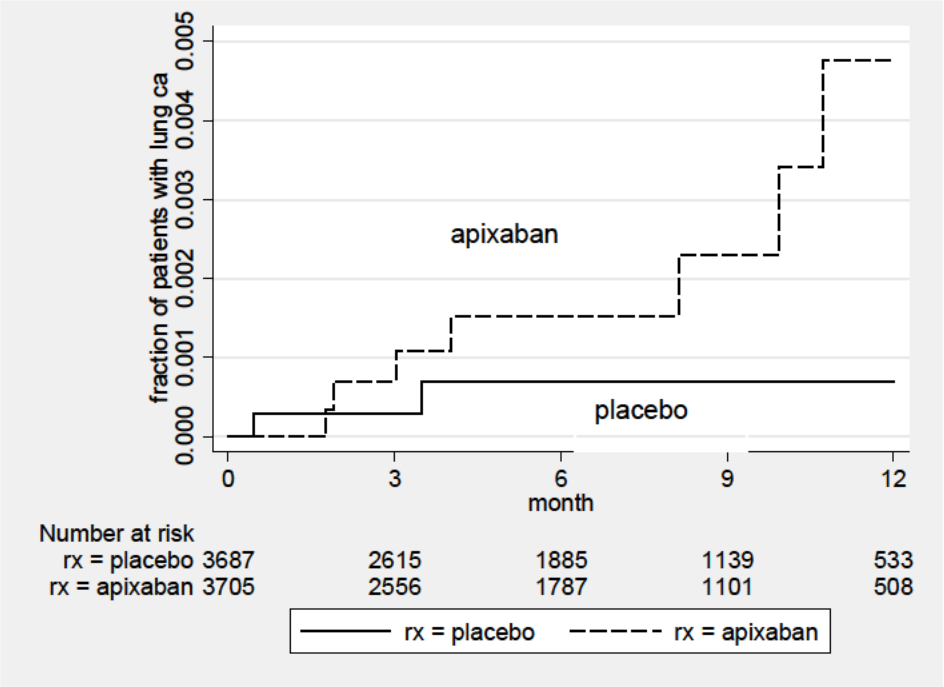
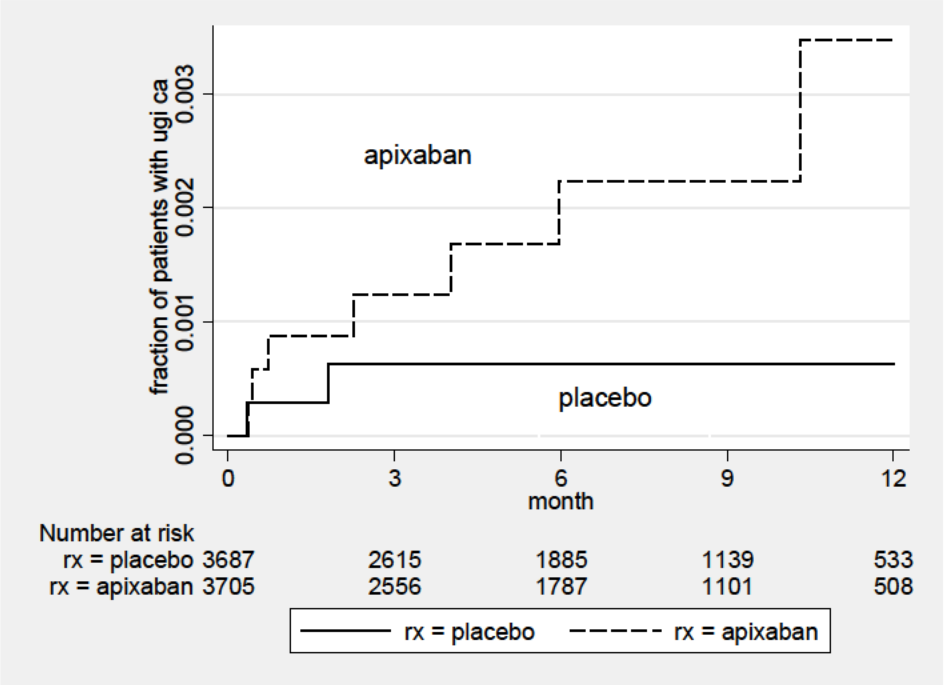


Figure 16: Upper GI Cancer Incidence in APPRAISE



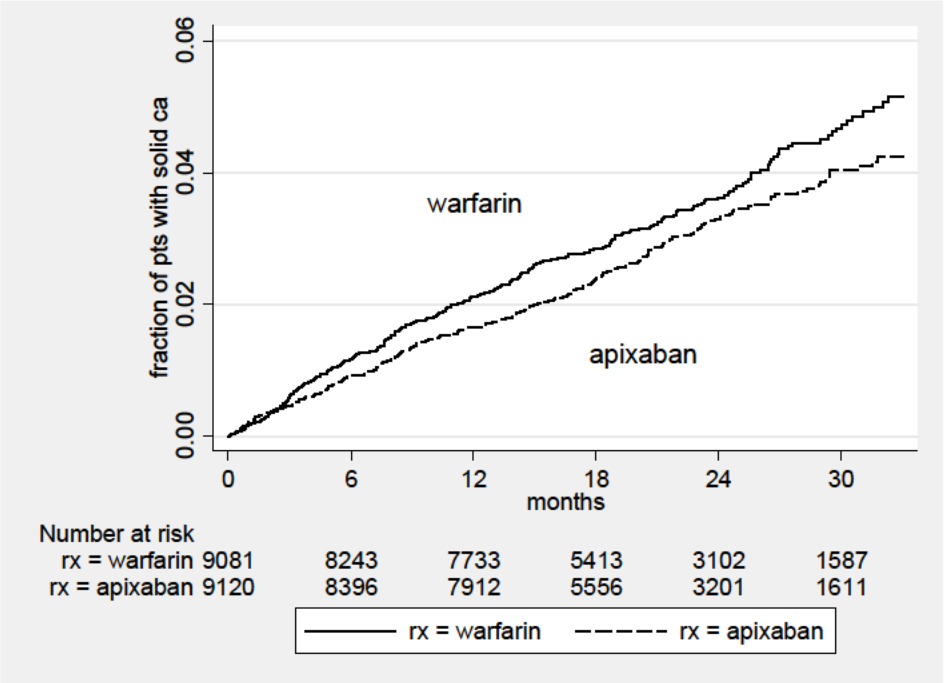
Bladder cancer detection began early in the apixaban arm, suggesting a detection effect rather than tumor promotion. They were not found in the placebo arm, and similarly lung and UGI cancers were rare in the placebo arm, with a low solid cancer incidence rate in APPRAISE compared to many other studies. While rates for these three cancer sites all diverged early they continued to diverge for the duration of the study and lung cancer rate divergence appeared to accelerate.

COMMENT: The APPRAISE solid cancer results do suggest an early detection effect because of bleeding. Because of its short duration, APPRAISE is not optimal for discriminating between an early detection effect only and the addition of a cancer promotion effect. Regardless, APPRAISE does support an association between bleeding and cancer, particularly considering the ARISTOTLE results I present next.

ARISTOTLE

ARISTOTLE was a trial of apixaban vs. warfarin in atrial fibrillation (afib) patients. Because apixaban was not added to standard antiplatelet therapy as in APPRAISE, bleed rates in ARISTOTLE were higher in the warfarin arm than in the apixaban arm. Correspondingly solid cancer rates were higher in the warfarin arm. I show the solid cancer event incidence curves for ARISTOTLE in Figure 17.

Figure 17: Solid Cancer Event Incidence in ARISTOTLE



While the divergence of the curves may not be extreme, the difference is borderline statistically significant for the ITT period (HR 0.85, 95% CI 0.72-1.00, p = 0.052) and is nominally significant for all reported cancers (p = 0.034).

I show the solid cancer sites in ARISTOTLE in Table 17.

Table 17: Solid Cancer Sites in ARISTOTLE

	warfarin	apixaban
anus	1	0
bile duct	5	4
bladder	34	25
breast	23	24
carcinoid	2	0
cervix	3	0
colon	45	47
esophagus	2	3
gi other	2	0
head & neck	9	8
kidney	12	9
liver	3	4
lung	39	36
melanoma	17	17
mesothelioma	0	1
other	1	0
ovary	3	2
pancreas	16	10
prostate	47	41
sarcoma	4	2
stomach	11	10
thyroid	4	2
unknown	13	8
uterus	5	6
vulva	0	1
total	301	260

The sites that are most differentiated between the two arms are bladder and pancreas. I show the incidence curves for bladder cancer events in Figure 18 and for pancreas cancer events in Figure 19.

Figure 18: Bladder Cancer Event Incidence in ARISTOTLE

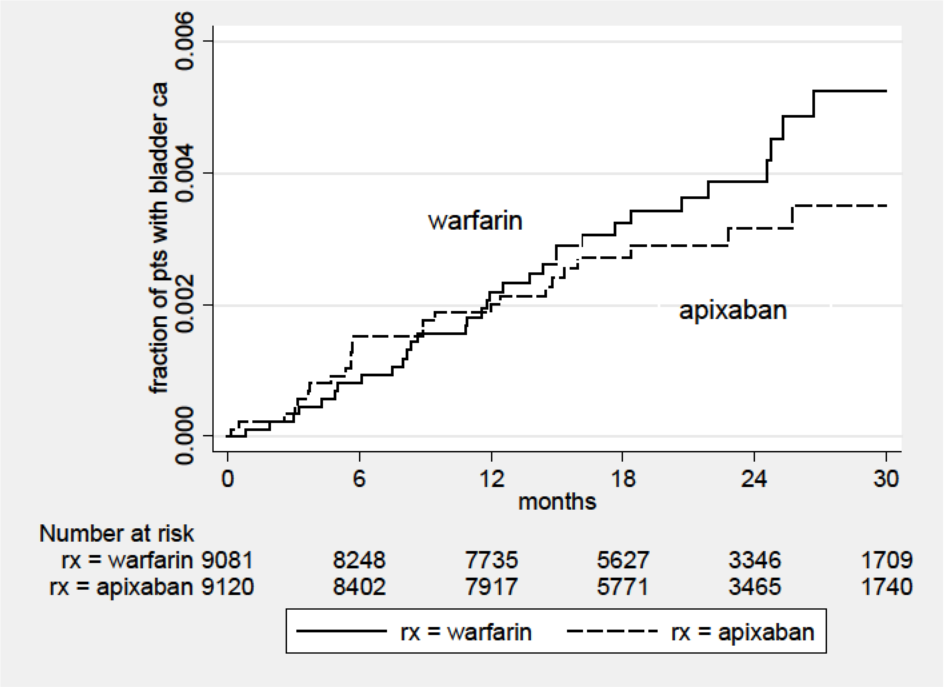
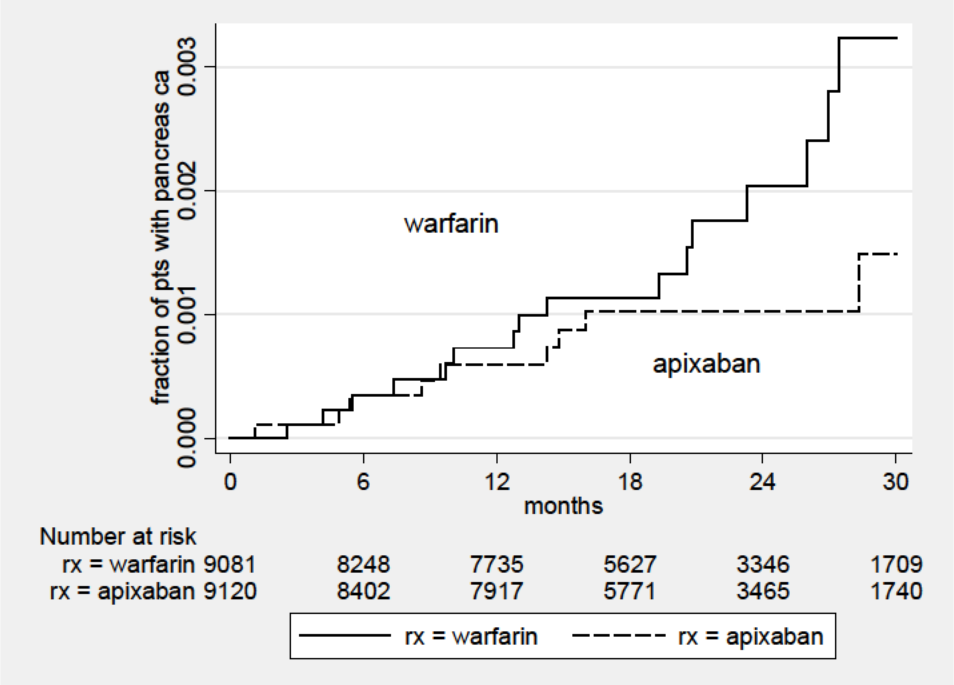


Figure 19: Pancreas Cancer Event Incidence in ARISTOTLE



Both curves diverge late, about 18 months.

COMMENT: The late divergence of the bladder and pancreas curves in ARISTOTLE suggest that the etiology is not an early detection bias but a real cancer promotion. The comparison of the APPRAISE and ARISTOTLE results suggest that the cancer promotion is related to inhibition of coagulation, rather than inhibition of a specific receptor.

AVERROES

AVERROES was a trial in afib patients of apixaban vs. aspirin. Major bleeding was little different between the two arms and solid cancer rates were little different between the two arms. Non-CV mortality was lower in the apixaban arm. AVERROES is consistent with no difference in bleeding associated with no difference in solid cancers but otherwise does not appear informative for this issue.

ATLAS

ATLAS was a trial in ACS patients of rivaroxaban vs. placebo added on to standard antiplatelet therapy. ATLAS had three arms for two dosages of rivaroxaban (2.5 or 5 mg BID) and placebo, with 1:1:1 randomization. Hence there were about 5,000 patients per arm.

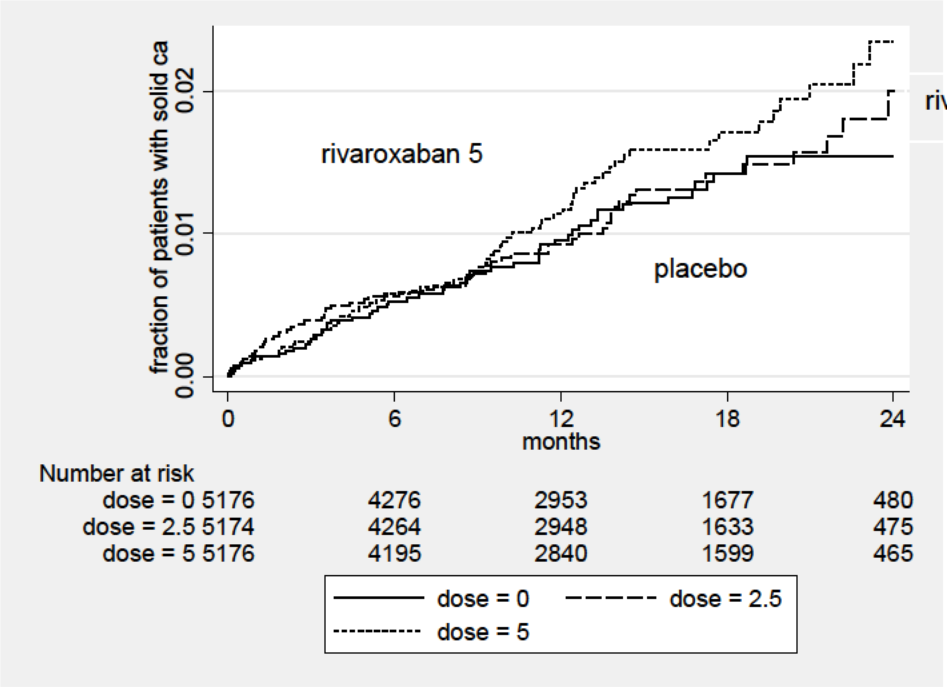
ATLAS had study conduct problems as detailed in my review of it. Follow-up was incomplete and mortality was lowest in the 2.5 mg arm but similar in the placebo and the 5 mg arms. Despite the conduct problems ATLAS had a higher rate of major bleeding in the rivaroxaban arms associated with higher rates of solid cancers and CV mortality in those arms compared to the placebo arm, although the differences in solid cancers and CV mortality are not statistically significant.

The two rivaroxaban dosages show an apparent dose-response for bleeding and solid cancers: The RRs for major bleeding were 2.1 and 2.5 respectively for the low and high dosages. The RRs for solid cancers were 1.1 and 1.3 respectively. There may also be a dose-response for non-CV mortality with RRs of 0.6 and 1.4 respectively. Note that the all-cause mortality was exceptionally low in the low dose (2.5 mg BID) group and appears anomalous as discussed in my review of ATLAS.

About 60% of patients in ATLAS had an initial invasive strategy, the vast majority being PCIs. There was no interaction between treatment or dose and an initial invasive strategy for solid cancers. The subgroup of patients managed medically actually had a higher RR point estimate for solid cancers than the invasive group (1.3 vs. 1.1), although all point estimates have wide confidence limits.

I show the solid cancer event incidence curves for ATLAS in Figure 20.

Figure 20: Solid Cancer Event Incidence in ATLAS



The solid cancer event incidence curves for placebo and rivaroxaban 2.5 mg are virtually superimposed (except at study end when numbers of patients at risk are low) while the curve for 5 mg starts to diverge at about 9 months and continues to separate for the rest of the study. I show the solid cancer sites in Table 18.

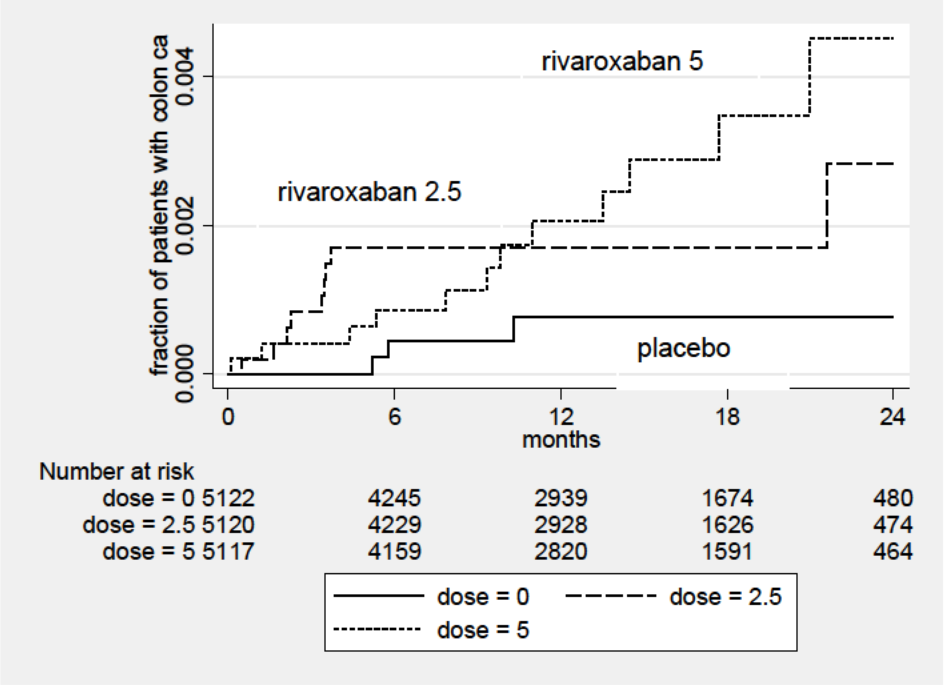
Table 18: Solid Cancer Sites in ATLAS

	placebo	rivaroxaban		
		2.5	5	any/2
bile duct	0	0	2	1
bladder	6	10	6	8
breast	3	5	5	5
cervix	2	0	0	0
colon	4	9	14	11.5
esophagus	0	1	1	1
head & neck	3	2	0	1
kidney	4	1	1	1
liver	1	0	1	0.5
lung	10	8	12	10
melanoma	0	2	3	2.5
mesothelioma	0	2	0	1
other	1	1	0	0.5
ovary	1	0	1	0.5

	placebo	rivaroxaban		
		2.5	5	any/2
pancreas	2	4	4	4
prostate	5	4	9	6.5
sarcoma	0	1	0	0.5
stomach	6	1	5	3
testes	0	0	1	0.5
thyroid	1	0	0	0
unknown	1	3	3	3
uterus	3	2	0	1
vagina	0	2	0	1
total	53	58	68	63

The cancer site that shows the greatest differentiation between rivaroxaban and placebo and dose-response is colon. I show the incidence curves for colon cancer events in Figure 21.

Figure 21: Colon Cancer Event Incidence in ATLAS



Particularly the 2.5 mg arm appears to show an early detection effect for colon cancers while the incidence curve for the 5 mg arm diverges more from the placebo curve starting about 9-10 months and diverges greatly thereafter.

COMMENT: While the solid cancer differences in ATLAS are not statistically significant, directionally they and the bleeding differences are consistent with those seen in APPRAISE, the other ACS trial of an anticoagulant added to standard antiplatelet therapy. APPRAISE may

show a more pronounced difference in cancer rates because of the older ages enrolled in APPRAISE compared to ATLAS (median age 67 vs. 61). The bleeding/cancer association of APPRAISE/ATLAS also is consistent with that seen in the antiplatelet ACS trials TRITON/TRACER and the clopidogrel trial CREDO in PCI. In fact, among the six trials with a majority (or close to majority) invasive component, only PLATO does not show an association of increased bleeding with increased solid cancers arguably because PLATO did not show much difference in bleeding rates between its arms—and its study conduct issues also may have obscured a small association and ticagrelor is not a thienopyridine. TRILOGY is the one ACS trial that does not confirm a bleeding-cancer association despite having higher somewhat higher major bleeding in its prasugrel arm but TRILOGY, like PLATO, also had serious conduct problems.

TRA2P, while not an ACS trial, is the one recent large cardiac outcome trial that does not demonstrate an association between bleeding and solid cancer. While apparently discordant with the invasive ACS trials, its results are consistent with the older, non-ACS cardiac outcome trials of clopidogrel having differentiated bleeding rates, i.e., CHARISMA, CURE, and ACTIVE-A. (See Table 10*.) I do not have a validated explanation for why the TRA2P and CHARISMA results for bleeding and solid cancers are quite different from those for CREDO, TRITON, TRACER, APPRAISE, and ATLAS. I can speculate that one possibility is the radiation exposure with the fluoroscopy during cardiac angiography and angioplasty. While it is not high relative to the levels required for DNA damage associated with initiation of carcinogenesis, I don't think we know whether it can affect immune function—and cardiac fluoroscopy irradiates the entire blood volume as well as the thymus. Do the antiplatelet drugs require a two-hit mechanism (irradiation and their inhibition) to achieve cancer promotion? Currently this latter mechanism is speculative. Another possible explanation is more mundane: Do the invasive trials have more complete solid cancer ascertainment, possibly from more chest imaging detecting more lung cancers and cancers metastatic to the lung?*

ROCKET

ROCKET was a trial in afib patients of rivaroxaban vs. warfarin. Its results are neutral for major bleeding, solid cancers, and non-CV mortality. These results support the hypothesis that the critical mechanism for cancer promotion is an effect upon coagulation rather than some other off-target effect.

J-ROCKET

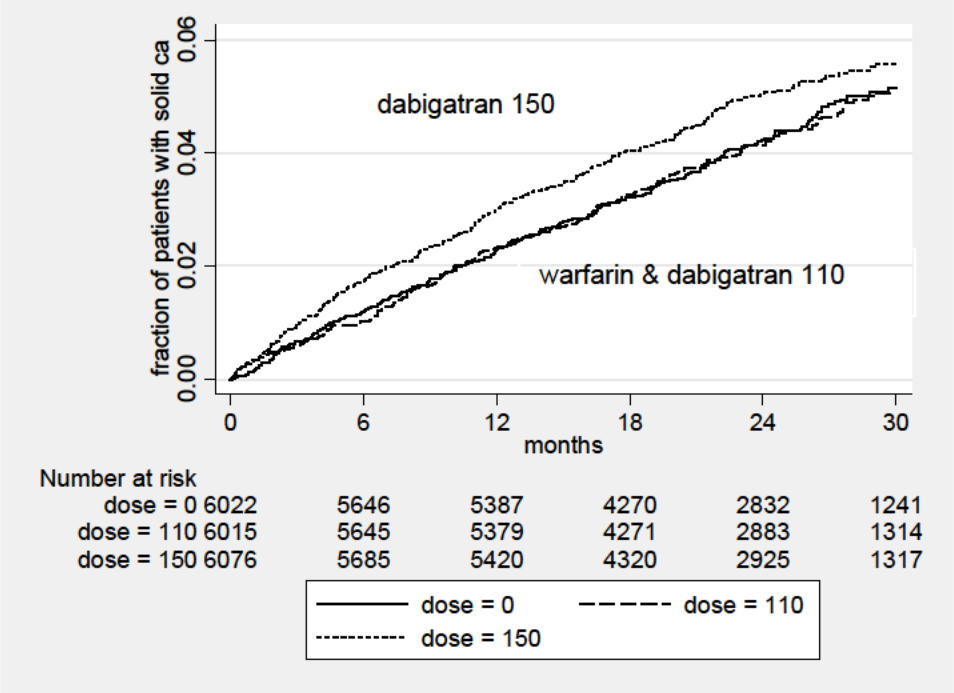
J-ROCKET was the Japanese version of ROCKET. I interpret it as similar to ROCKET. While the point estimate for the non-CV death RR looks impressive (0.3), it is based on a total of 9 non-CV deaths so its confidence interval is extremely wide. Note that J-ROCKET was performed in an elderly Asian population and did report a substantial rate of solid cancers (1.9/100 PEY.) The sites with highest incidence were colon and stomach and accounted for 57% of the first solid cancer events. Compare the 1.9/100 PEY incidence in J-ROCKET to the 0.2/100 PEY incidence in the Asian subgroup of TRILOGY.

RELY

RELY was a trial in afib patients of two doses of dabigatran (110 and 150 mg BID blinded) vs. open label warfarin. The combined doses had slightly less major bleeding than warfarin and slightly more solid cancers. However, the statistics in Table 15 do not convey all of the specific findings in RELY both because they aren't differentiated by dose and because dabigatran caused a different pattern of bleeding than warfarin.

Major bleeding was lower in the 110 mg arm (RR 0.8) than in the 150 mg arm (RR 0.9). However, GI bleeding was higher with dabigatran than with warfarin, slightly for GI bleed SAEs in the 110 mg arm (RR 1.1) and significantly higher in the 150 mg arm (RR 1.5). Solid cancer events were similar in frequency to warfarin in the 110 mg arm (RR 1.0) but more frequent in the 150 mg arm (RR 1.2).

Figure 22: Solid Cancer Event Incidence in RELY



The 150 mg arm had a higher rate of solid cancers than either the 110 mg arm or the warfarin arm, but there appears to be some convergence of the rates late.

I show the solid cancer sites in Table 19.

Table 19: Solid Cancer Sites in RELY

	warfarin	dabigatran		
		110	150	any/2
anus	0	0	2	1
bile duct	2	2	8	5
bladder	32	17	31	24

	warfarin	dabigatran		
		110	150	any/2
breast	17	21	27	24
carcinoid	1	0	0	0
cervix	1	1	0	0.5
colon	32	45	51	48
esophagus	3	10	6	8
gi other	1	1	2	1.5
head & neck	7	12	9	10.5
kidney	11	8	11	9.5
liver	6	1	3	2
lung	37	36	37	36.5
melanoma	14	15	17	16
mesothelioma	0	0	1	0.5
ovary	1	2	2	2
pancreas	10	9	8	8.5
penis	1	1	1	1
prostate	45	41	43	42
sarcoma	2	0	0	0
stomach	6	7	6	6.5
testes	0	0	1	0.5
thyroid	1	1	3	2
unknown	5	4	8	6
uterus	2	3	3	3
total	237	237	280	258.5

The sites that were more frequent in the dabigatran arm were bile duct, breast, colon, and esophagus while bladder and liver were more frequent in the warfarin arm. I show the breast cancer event incidence curves in Figure 23, the colon cancer event incidence curves in Figure 24, the esophagus event incidence curves in Figure 25, the bladder cancer event incidence curves in Figure 26, and the liver/bile duct cancer incidence curves in Figure 27. (Liver and bile duct cancers were rare and are frequently lumped in analyses, so I did so for the incidence curves.)

Figure 23: Breast Cancer Event Incidence in RELY

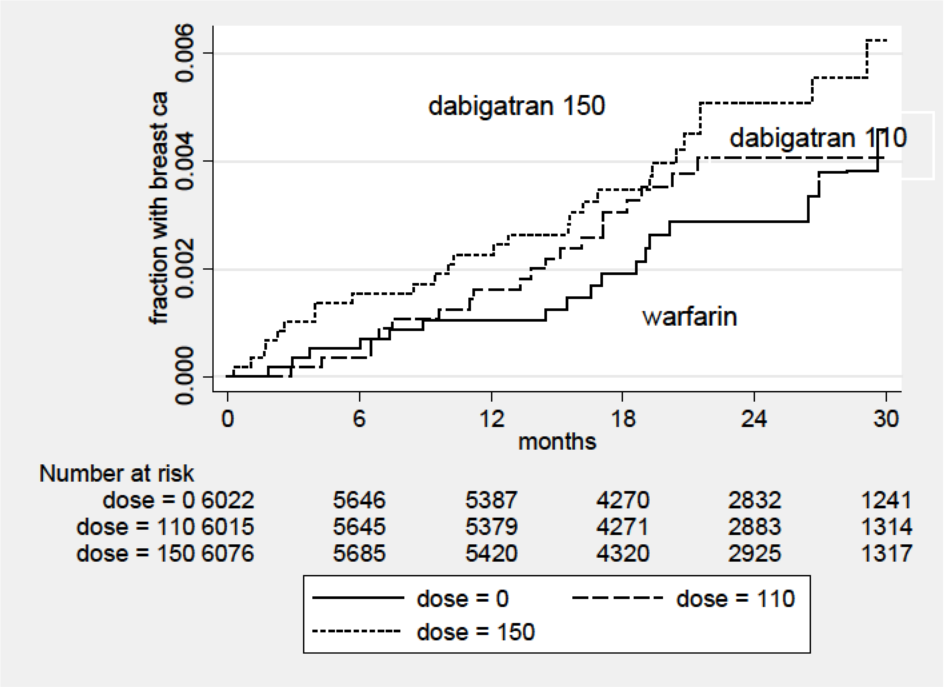


Figure 24: Colon Cancer Event Incidence in RELY

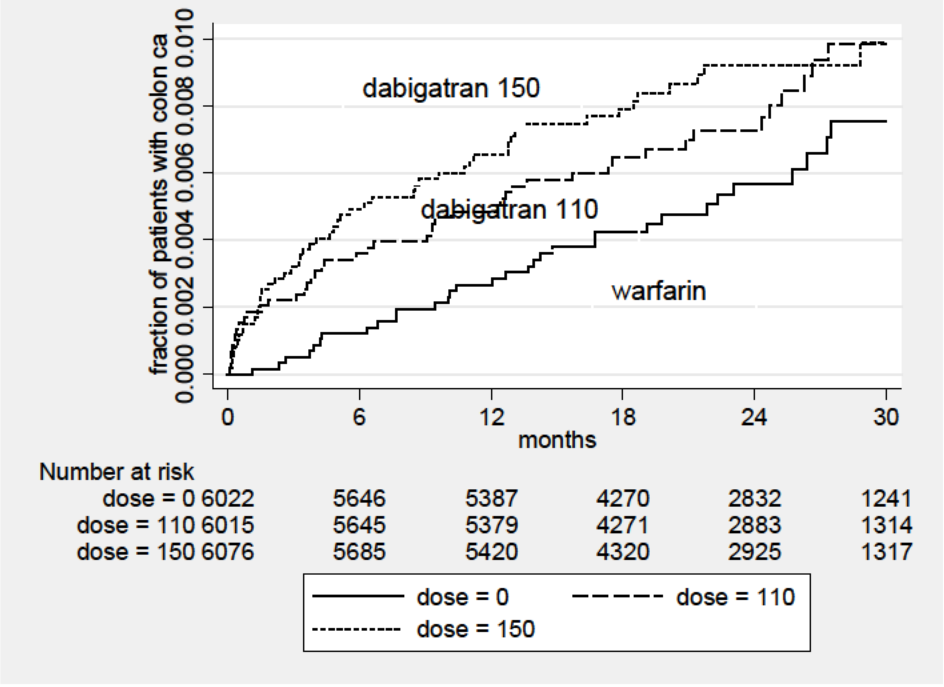


Figure 25: Esophagus Cancer Event Incidence in RELY

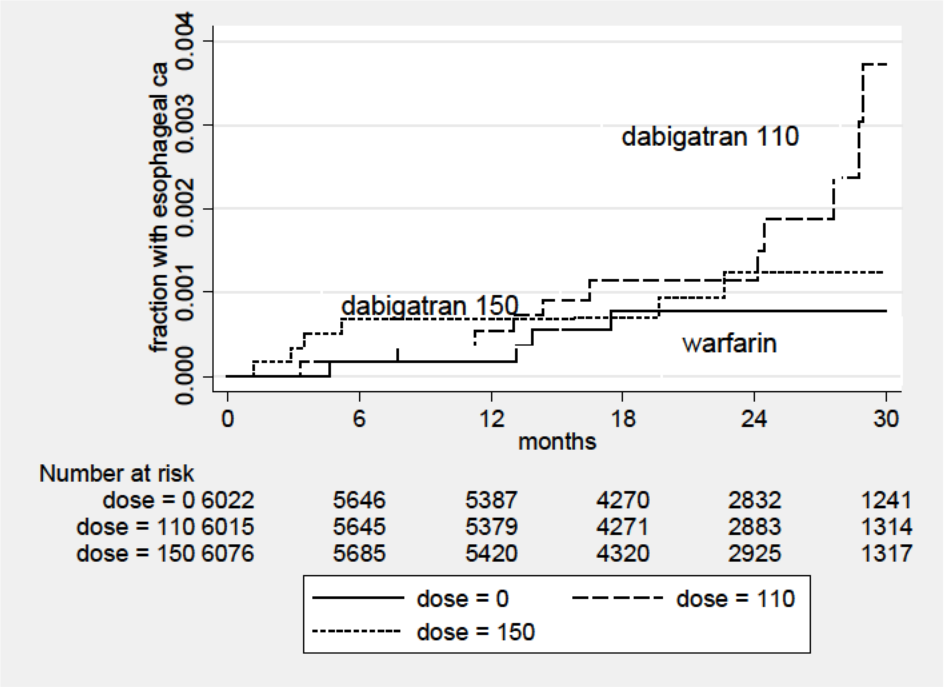


Figure 26: Bladder Cancer Incidence in Rely

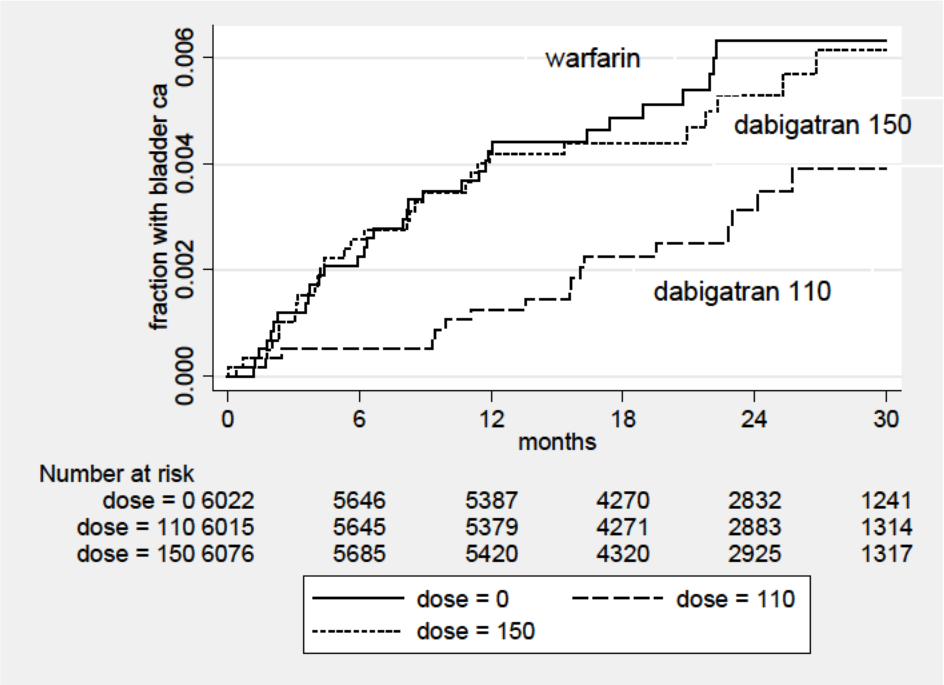
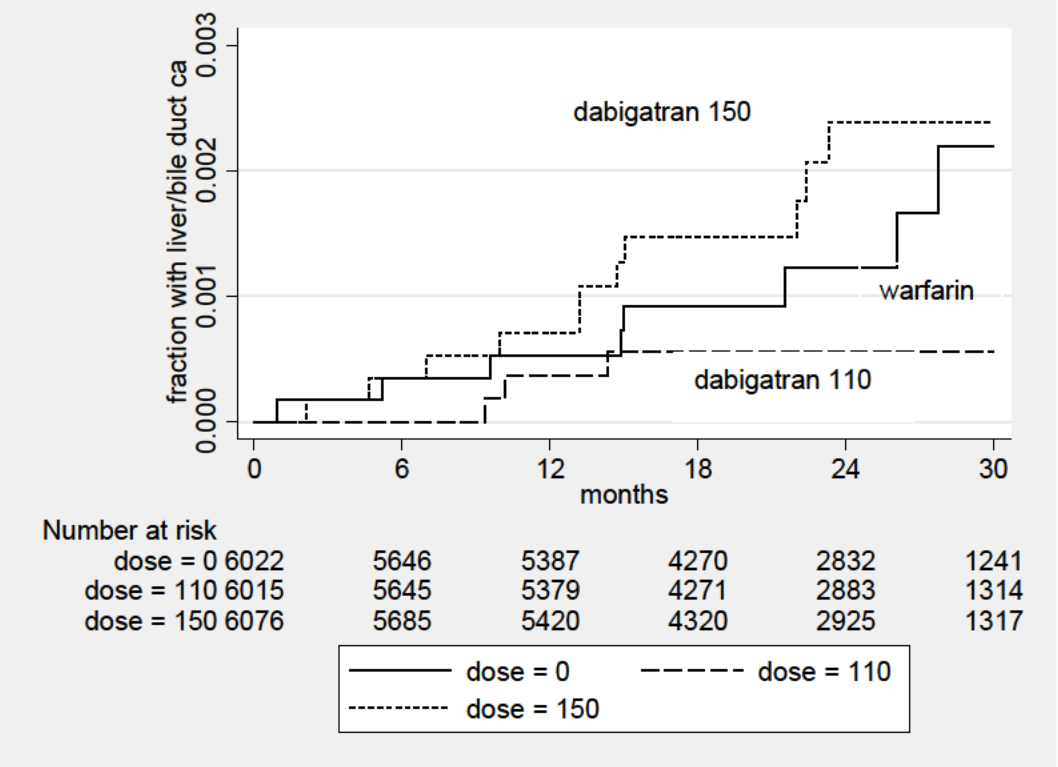


Figure 27: Liver/Bile Duct Cancer Incidence in RELY



While the site-specific cancer incidence curves have the limitation that the numbers are so and variability is high, there do appear to be several patterns:

- The breast and esophagus cancer incidence curve suggest similar, higher rates than warfarin for both doses. Whether these are real differences or chance variation cannot be distinguished definitively from this size study. The esophagus cancer increase late appears relevant because one established dabigatran adverse effect is GI irritation. If this increase in esophagus cancer is real the late disparity between the doses would likely be the result of chance.

- The colon cancer incidence curves for both doses diverge early, show greater effects at the higher dose, and converge somewhat with each other and warfarin at about 24 months. The early divergence and later convergence suggest that the colon cancer effects are detection biases resulting from the increased GI bleeding with dabigatran, likely do to active dabigatran in the gut (while warfarin's site of action is the liver.)

- Warfarin and the high dose share similar incidence curves for bladder and liver/bile duct cancer. They also share similar overall bleeding profiles (excluding the increased GI bleeding with dabigatran.) The bladder cancer incidence curves also suggest an early detection effect.

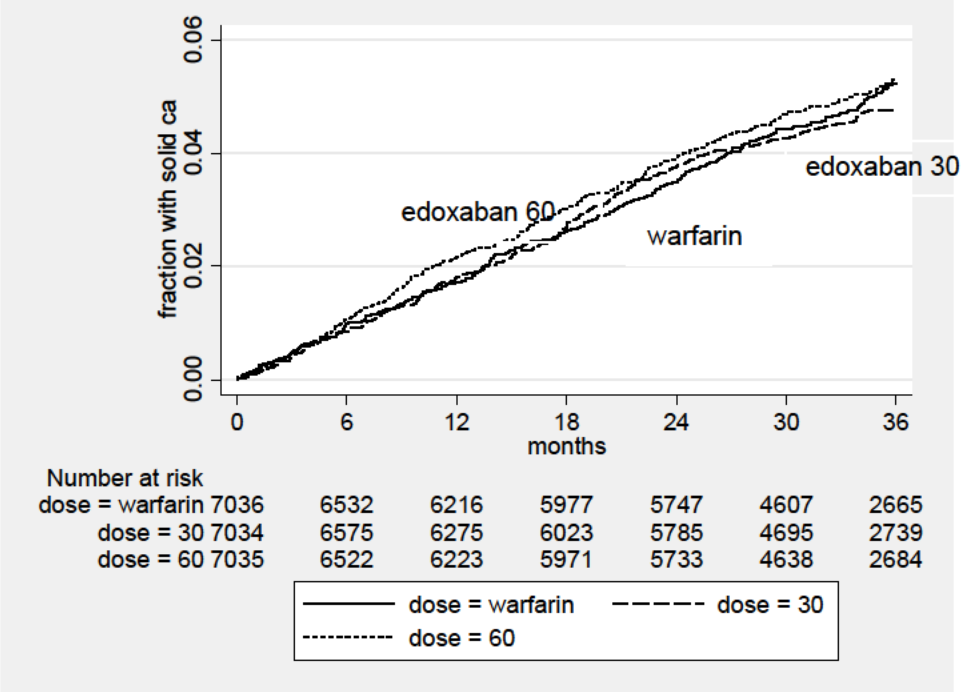
COMMENT: RELY supports both an early detection effect and increased solid cancers with increased bleeding. It also suggests that some drugs may have additional mechanisms operative, e.g., the possible increase in esophagus cancer with dabigatran.

ENGAGE

ENGAGE was a trial in afib patients of two dosages of edoxaban (30 and 60 mg QD) vs. warfarin. Hence, as for RELY, the statistics in Table 15 do not convey completely the ENGAGE findings. Furthermore, the median duration of follow-up was long (34 months) but edoxaban premature discontinuation was high (34%) and completeness of follow-up was marginal (90%). These latter two statistics limit the validity of ENGAGE for informing regarding cancer associations.

ENGAGE, also like RELY, had less overall bleeding in the new drug arms (RRs 0.5 and 0.8) than in the warfarin arm. GI bleeding in ENGAGE was a variation on the RELY rates: the 30 mg arm had less bleeding (RR 0.7) than the warfarin arm but the 60 mg arm had slightly more bleeding (RR 1.2) than the warfarin arm. Solid cancer rates were not differentiated by arm, as shown by the incidence curve in Figure 28.

Figure 28: Solid Cancer Event Incidence in ENGAGE



There are some site-specific incidence curves that appear informative. I show the cancer event incidence curves for colon cancer in Figure 29, for esophagus cancer in Figure 30, for lung cancer in Figure 31, and for pancreas cancer in Figure 32.

Figure 29: Colon Cancer Event Incidence in ENGAGE

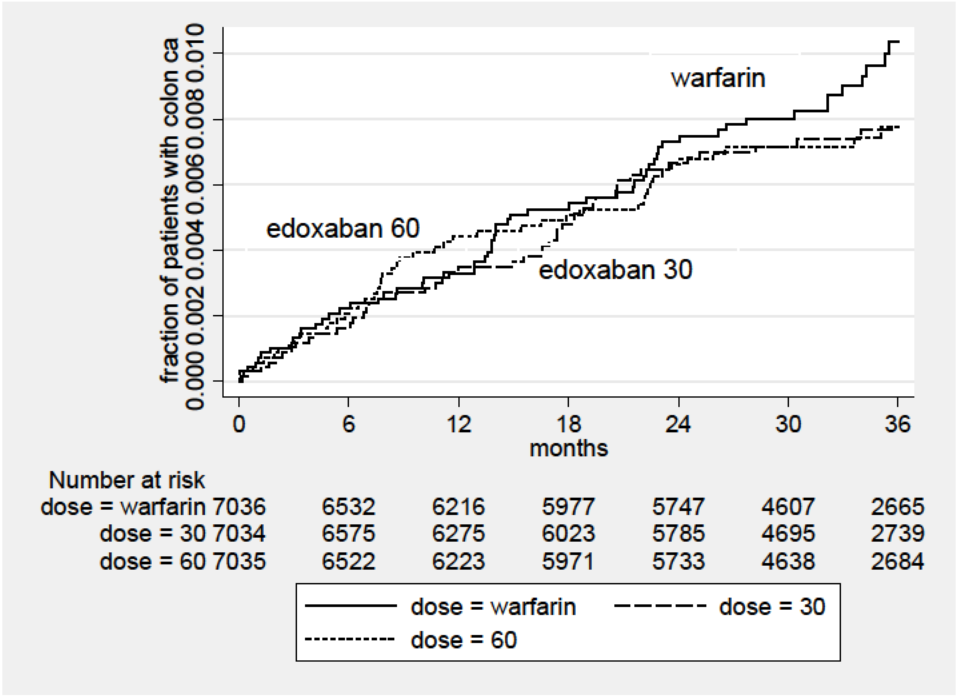


Figure 30: Esophagus Cancer Event Incidence in ENGAGE

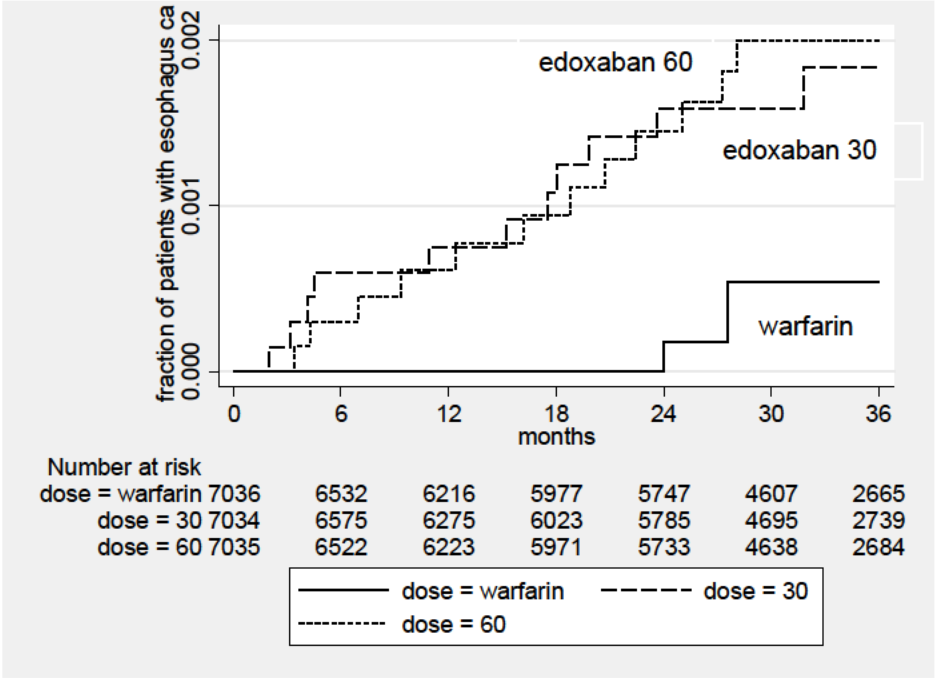


Figure 31: Lung Cancer Event Incidence in ENGAGE

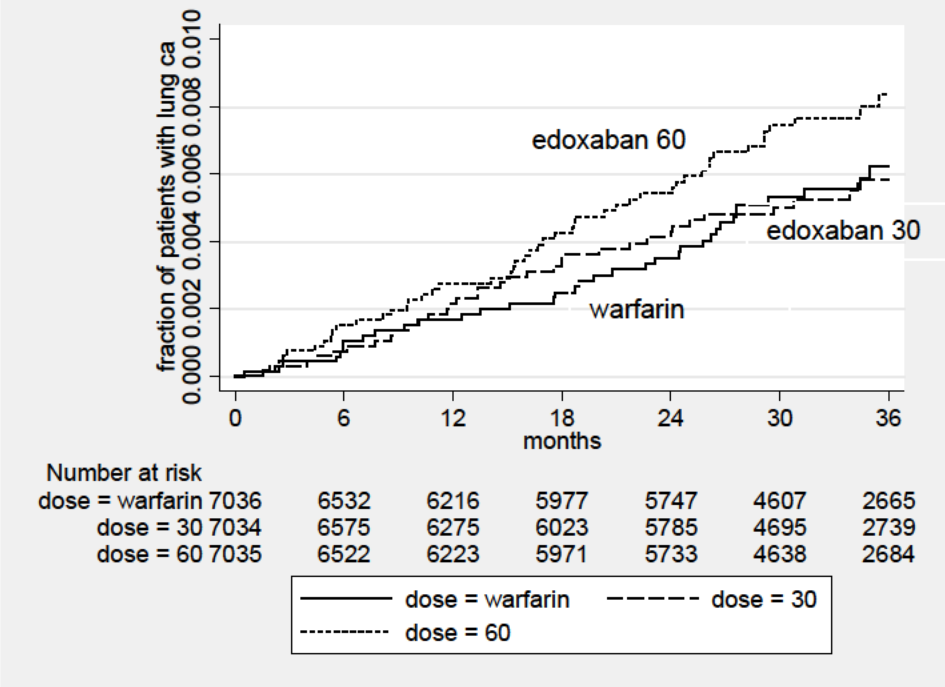
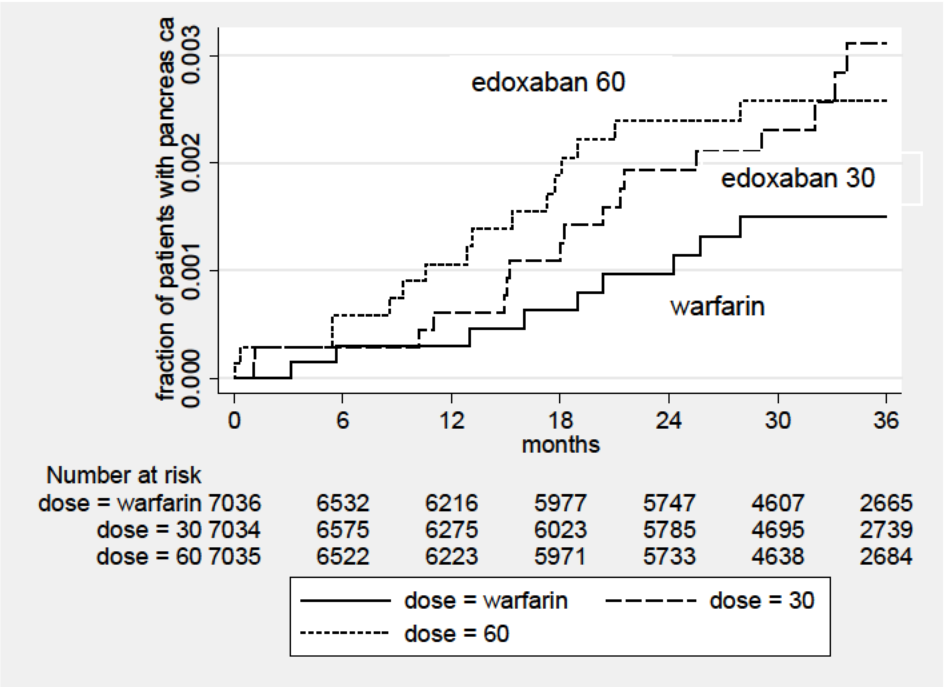


Figure 32: Pancreas Cancer Event Incidence in ENGAGE



I have the following observations about the site-specific cancer incidence curves:

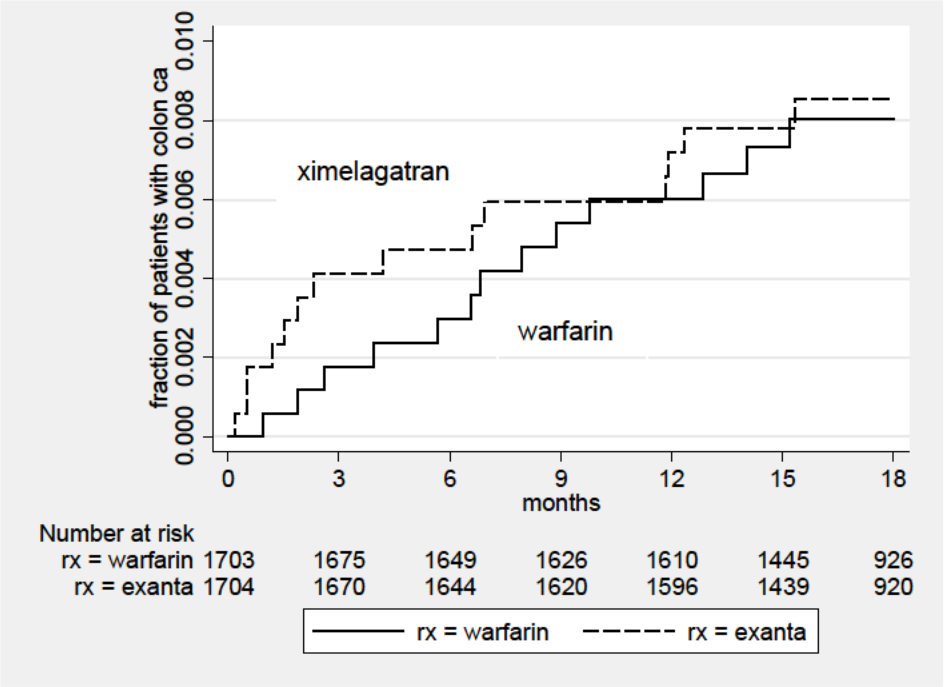
- Colon cancer was not differentiated by arm, despite the differences in GI bleeding. However, there was also no suggestion of an early detection bias.
- Esophagus cancer incidence was much higher and similar in both edoxaban arms. The incidence curves start diverging early from warfarin's. While one would be tempted to dismiss the differentiation as chance, the fact that both edoxaban arms are similar and the differentiation of esophagus cancer with dabigatran (although with a difference time course), suggests that we shouldn't dismiss this finding.
- Lung and pancreas cancer incidence is differentiated from warfarin with edoxaban, although the higher lung cancer incidence is only for the 60 mg arm. These two sites have also shown high rates with other NOACs.

COMMENT: The ENGAGE cancer results by themselves are not impressive. However, some differences appear consistent with other NOACs. ENGAGE raises the question of how much of the effect upon cancers is dependent upon local levels of the drug or transport into cells rather than measured plasma drug levels. ENGAGE suggests it is possible for the comparison of two anticoagulants to have one promote cancers at some sites and the other promote cancers at other sites depending upon different drug activations and distributions.

SPORTIF III

SPORTIF III was an unblinded trial in afib patients of ximelagatran (Exanta), a direct thrombin inhibitor, vs. warfarin. SPORTIF III was conducted outside of the U.S. while its sister trial, SPORTIF V, was conducted double-blind in the U.S. In SPORTIF III major bleeding was lower in the ximelagatran arm, as were non-CV deaths, while solid cancer event rates were similar in the two arms. While overall solid cancer events were evenly distributed between the two arms, there are two notable imbalances in specific sites: bladder cancers were reported only in the warfarin arm (5 vs. 0) while esophagus cancers were only reported in the ximelagatran arm (3 vs. 0). Colon cancers events were evenly balanced between the two arms with incidence curves as shown in Figure 33.

Figure 33: Colon Cancer Event Incidence in SPORTIF III



SPORTIF III appears to show an early detection bias in the ximelagatran arm despite GI bleeds reported as balanced between the two arms.

COMMENT: Figure 33 provides an estimate of how long an early detection bias may suggest an imbalance in cancer rates. By 9 months the colon cancer rates were equalized. However, SPORTIF V gives a different picture of colon cancer (see Figure 35) in a ximelagatran vs. warfarin study. The difference may be due to the long duration and higher cancer rates in SPORTIF V. On the other hand, the differences in small numbers of bladder cancers, with opposite directions in SPORTIF III and SPORTIF V would appear to be the play of chance. The difference in esophagus cancers, while also small, seems more suggestive because of the esophagus cancer findings in SPORTIF V and with dabigatran and edoxaban.

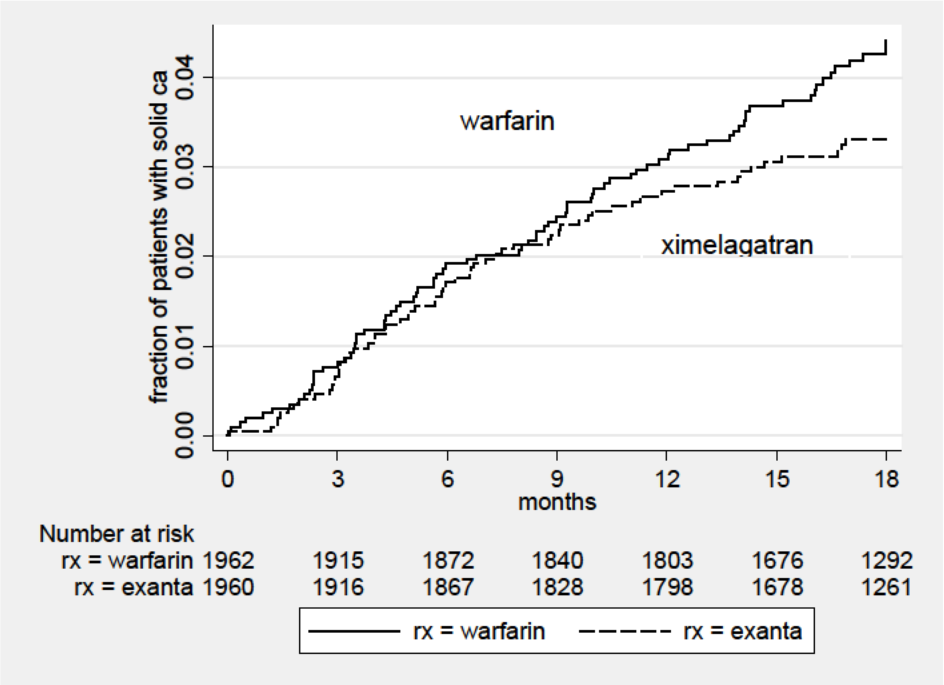
SPORTIF V

SPORTIF V was the double-blind, U.S. and Canada trial in afib patients of ximelagatran, a direct thrombin inhibitor, vs. warfarin. SPORTIF V is the sister trial to the unblinded SPORTIF III trial outside the U.S. SPORTIF V and SPORTIF III had nearly identical protocols with similar eligibility criteria. However, although not a topic for this review, SPORTIF V (the unblinded trial) produced a point estimate for the primary endpoint (stroke plus systemic embolic events) favorable to ximelagatran while SPORTIF III (the blinded trial) produced a primary endpoint point estimate unfavorable to ximelagatran. For purposes of evaluating cancers SPORTIF V had higher enrollment, higher cancer rates, and a longer duration of follow-up than SPORTIF III, resulting in more cancer events in SPORTIF V than in III.

SPORTIF V, like III, reported fewer major bleeds and non-CV deaths with ximelagatran (RR about 0.7 for each). SPORTIF V, however, reported slightly more GI bleeds with ximelagatran

(RR about 1.1) and a slightly lower solid cancer event incidence with ximelagatran (RR 0.8). I show the solid cancer event incidence curves for SPORTIF V in Figure 34.

Figure 34: Solid Cancer Event Incidence in SPORTIF V



While not statistically significant by the usual tests, the curves start to diverge at about 8 months and continue to diverge until the end of study. There were several sites with substantial differences by arm as show in Table 20.

Table 20: Solid Cancer Sites in SPORTIF V

	warfarin	ximelagatran
bladder	5	9
breast	11	2
carcinoid	1	0
cervix	0	1
colon	8	15
esophagus	0	2
head & neck	3	1
kidney	2	2
liver	1	0
lung	14	14
melanoma	8	4
mesothelioma	1	0
pancreas	1	1

	warfarin	ximelagatran
prostate	21	13
sarcoma	2	1
stomach	1	2
thyroid	1	0
unknown	2	0
uterus	1	1
vagina	1	0
total	84	68

The cancer sites with substantial differences by arm in SPORTIF V were bladder, breast, colon, melanoma, and prostate. Because bladder cancer went in opposite directions in SPORTIF III and SPORTIF V, I will not comment further regarding it. While not substantial, it is worth noting that esophagus cancer was only reported in the ximelagatran arm, as in SPORTIF V. Regarding the other sites with differences I show the cancer event incidence curves for colon cancer in Figure 33, for breast cancer in Figure 36, for melanoma in Figure 37, and for prostate cancer in Figure 38.

Figure 35: Colon Cancer Event Incidence in SPORTIF V

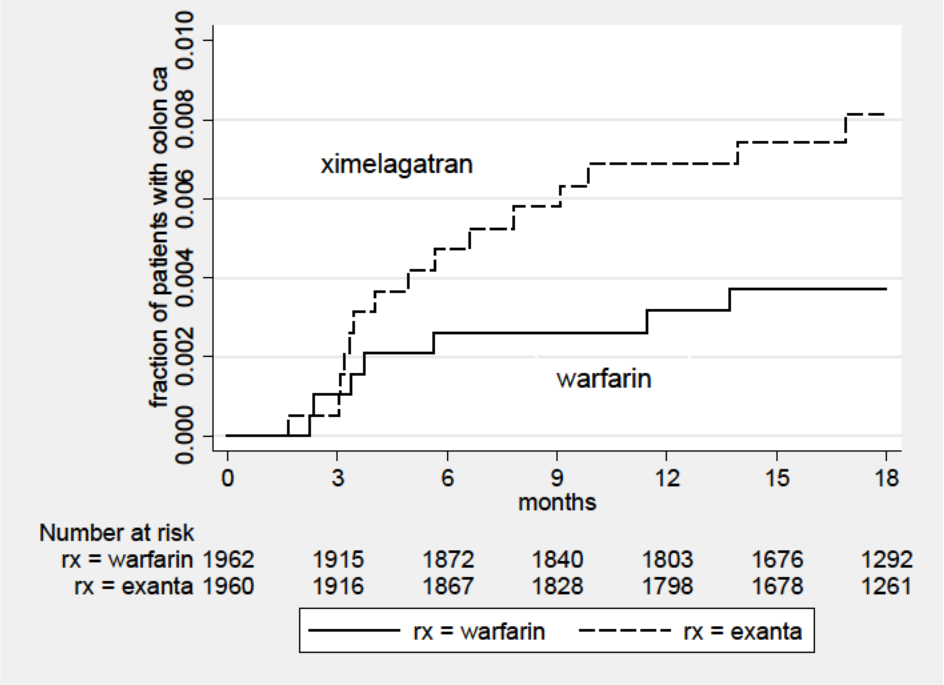


Figure 36: Breast Cancer Event Incidence in SPORTIF V

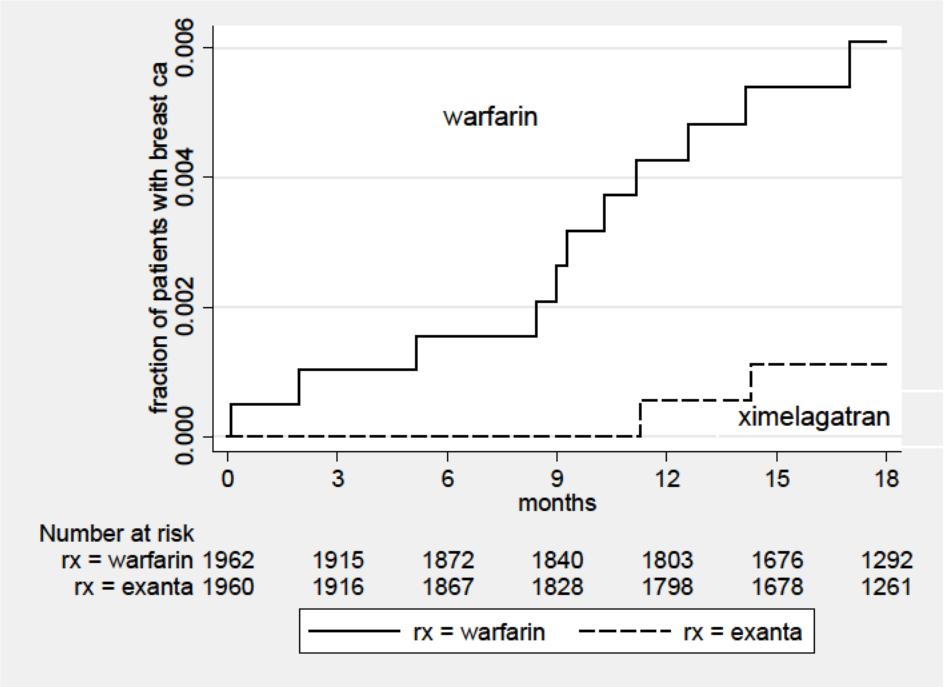


Figure 37: Melanoma Event Incidence in SPORTIF V

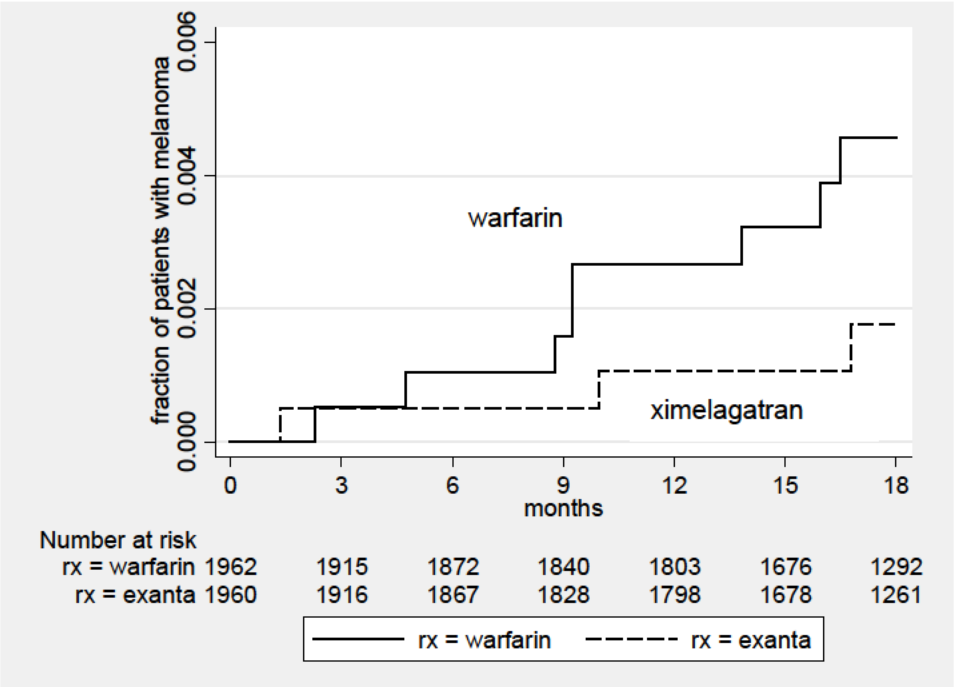
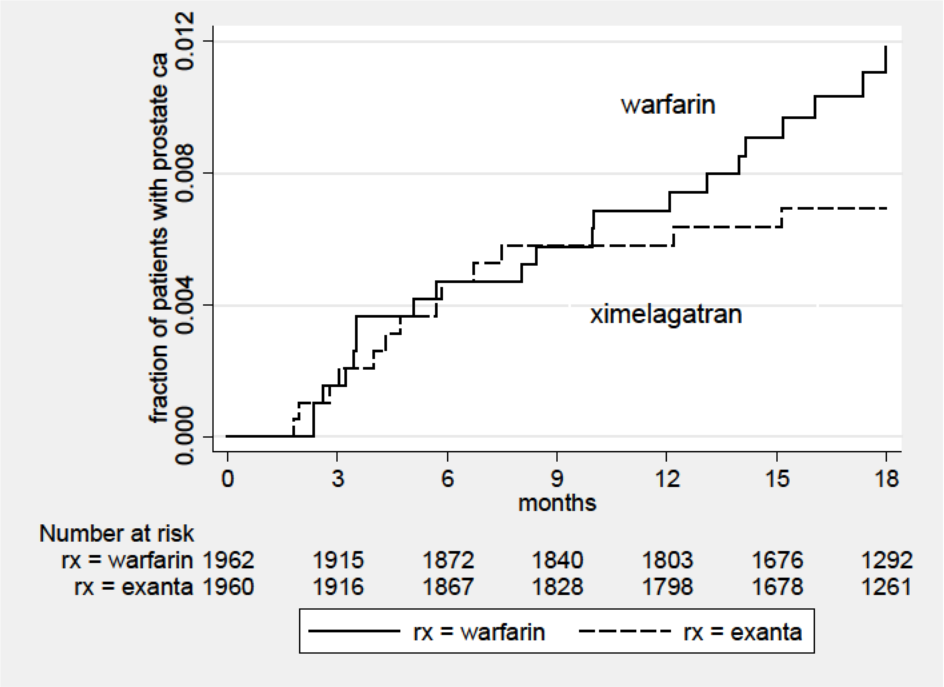


Figure 38: Prostate Cancer Event Incidence in SPORTIF V



I have the following observations regarding the site-specific cancer incidence curves:

- Colon cancer was more frequent with ximelagatran in SPORTIF V as it was initially in SPORTIF III, but the catch-up in the warfarin arm is incomplete in SPORTIF V.
- Breast cancer diverges quickly in the warfarin arm (3 cases), suggesting the random variation, but it also continues to diverge throughout the rest of the study.
- Prostate cancer and melanoma both have delayed divergences, more frequent with warfarin, after about 9 months. Because melanoma showed a nominal difference, I also examined non-melanoma skin cancer rates. Non-melanoma skin cancers were unusually highly reported, with more patients with non-melanoma skin cancers than with all other solid cancers combined. Non-melanoma skin cancers were slightly less frequent with ximelagatran (RR 0.86)—more frequent with warfarin—but not statistically significantly so. The incidence curves are more variable, i.e., diverging at 5 months, converging and 10 months, and then diverging slightly for the rest of the study.

COMMENT: SPORTIF V again demonstrates that, when warfarin produces more bleeding, it also is associated with more solid cancers. Of note is that ximelagatran in SPORTIF V produced more GI bleeding and is associated with more GI cancers (esophagus, stomach, and colon) than warfarin. While some of the latter difference may be early detection, the incidence curves diverge throughout the duration of the study.

References

ATBCCP_Study_Group (1994). "The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group." N Engl J Med **330**(15): 1029-35.

CDC (2014). LCWK1. Deaths, percent of total deaths, and death rates for the 15 leading causes of death in 5-year age groups, by race and sex: United States, 2011.

DAPT_Investigators (2014). DAPT Study Update 5Sep14, PowerPoint presentation.

DAPT_Investigators (2014). DAPT Study Update 17Sep14, PowerPoint presentation.

DAPT_Investigators (2014). DAPT Study Update 22Aug14, PowerPoint presentation.

DAPT_Investigators (2014). DAPT Study Update 24Oct14, PowerPoint presentation.

De Cicco, M. (2004). "The prothrombotic state in cancer: pathogenic mechanisms." Crit Rev Oncol Hematol **50**(3): 187-96.

FDA (2014). FDA Drug Safety Communication: FDA reviews long-term antiplatelet therapy as preliminary trial data shows benefits but a higher risk of non-cardiovascular death, 16Nov14.

Heywood, R., A. K. Palmer, et al. (1985). "The toxicity of beta-carotene." Toxicology **36**(2-3): 91-100.

Marciniak, T. A. (2009). Secondary Review of Cancer Adverse Events and Risk/Benefit, NDA 22-307, Prasugrel.

Marciniak, T. A. (2012). Analysis Plan for ARBs and Cancer.

Marciniak, T. A. (2013). Clinical Review Updated, Cancer in TRILOGY, NDA 22-307 S008, Prasugrel.

Marciniak, T. A. (2013). TSI 935 Clinical Review: Angiotensin receptor blockers (ARBs) Risk of cancer.

Mauri, L., D. J. Kereiakes, et al. (2010). "Rationale and design of the dual antiplatelet therapy study, a prospective, multicenter, randomized, double-blind trial to assess the effectiveness and safety of 12 versus 30 months of dual antiplatelet therapy in subjects undergoing percutaneous coronary intervention with either drug-eluting stent or bare metal stent placement for the treatment of coronary artery lesions." American Heart Journal **160**(6): 1035-1041.e1.

Mauri, L., D. J. Kereiakes, et al. (2014). "Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents." New England Journal of Medicine **23**(371): 2155-66.

.

Morrell, C. N., A. A. Aggrey, et al. (2014). "Emerging roles for platelets as immune and inflammatory cells." Blood **123**(18): 2759-67.

NCI. (2012). "Lung Cancer Prevention (PDQ®)." Retrieved May 1, 2013, from http://www.cancer.gov/cancertopics/pdq/prevention/lung/Patient/page3/print.

Omenn, G. S., G. E. Goodman, et al. (1996). "Risk factors for lung cancer and for intervention effects in CARET, the Beta-Carotene and Retinol Efficacy Trial." J Natl Cancer Inst **88**(21): 1550-9.

Peto, R., R. Doll, et al. (1981). "Can dietary beta-carotene materially reduce human cancer rates?" Nature **290**(5803): 201-8.

Rubin, B. A. (1964). "Carcinogen-induced tolerance to homotransplantation." Prog Exp Tumor Res **5**: 217-92.

Sipahi, I., S. M. Debanne, et al. (2010). "Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials." Lancet Oncol **11**(7): 627-36.

Southworth, M. R. (2014). TSI 1361 Clopidogrel and prasugrel and increased mortality Dual Antiplatelet Therapy Trial Results.

Southworth, M. R., N. Stockbridge, et al. (2013). TSI 935 Risk of cancer with angiotensin receptor blockers, Decisional Memo

.

Wachter, L. A. and M. R. Southworth (2014). TSI 1361 Meeting Memo 7Nov14.

DAPT
STUDY

STUDY UPDATE

22 August 2014

Agenda

1. Review of DAPT Stakeholder collaboration
2. Timeline
3. Communications
4. Confidentiality
5. Primary results (DES)
6. Ongoing analysis
7. Summary and discussion

Attendees

Study Leadership: Laura Mauri, MD, *PI,* Dean Kereiakes, MD, *co-PI*

HCRI: Priscilla Driscoll Shempp, *DAPT Study Project Director*

FDA

- **CRDH**: Andy Farb, MD, *Senior Medical Reviewer,* Bram Zuckerman, MD, *Director, FDA Division of Cardiovascular Devices*
- **CDER**: Mary Ross Southworth, PharmD, *Deputy Director of Safety, Division of Cardiovascular and Renal Products*

Device Manufacturers

- **Abbott**: Charles Simonton, MD, *Chief Medical Officer, Divisional VP, Med. Affairs*
- **Boston Scientific**: Peter Maurer, MPH *Director of Clinical Trials*
- **Cordis**: Patti Schleckser, *Director of Clinical Research*
- **Medtronic**: Sandeep Brar, MD, *Director of Clinical Research*

Pharmaceutical Manufacturers

- **Bristol-Myers Squibb**: Charlotte Jones-Burton, MD, *Director, CV Medical Strategy*
- **Daiichi Sankyo**: Elizabeth da Silva, MSc PhD, *Executive Director of Regulatory Affairs*
- **Eli Lilly**: LeRoy LeNarz, MD, *Sr. Medical Director – Cardiovascular*
- **Sanofi**: William Daley, MD, *VP of Business Development & Licensing*

REVIEW OF DAPT STAKEHOLDER COLLABORATION

Dual Antiplatelet Therapy Study

- Manufacturers recognized that a definitive trial would necessarily be large
- The FDA request resulted in a unique public-private collaboration among 4 manufacturers of DES and then current manufacturers of thienopyridine/antiplatelet medications
- June 2008 AdvaMed facilitated a proposal process from academic CROs along the parameters of basic trial specifications from FDA and industry
- July 2008 Harvard Clinical Research Institute submitted an operational plan and trial design to AdvaMed that was accepted
- September 2008 Harvard Clinical Research Institute submitted IDE
- October 2008 IDE approved
- August 2009 trial began enrollment
- July 2011 trial completed enrollment of 26,000 subjects worldwide
- Results to be presented November 2014

TIMELINES

Key Activities Up Through AHA

Key Dates	Milestone
August 22	Primary Endpoint Review with FDA
August 29	Product specific study data provided to each device manufacturer
September 17	Circulate manuscript drafts to manufacturers and FDA
September 29	Deadline for comments
October 1	Submit manuscripts for publication
November 16	“LBCT Presentation” : DES 30m vs 12m DAPT Primary Analysis
November 18	“Update on Randomized Trials”” DES vs BMS, and BMS 30m vs 12m DAPT

COMMUNICATIONS

DAPT Study Final Results Communications Goals

- Harvard Clinical Research Institute (HCRI), as the sponsor of the DAPT Study, is responsible for ensuring that all communications regarding the DAPT Study and its final results:
  - Meet all FDA guidelines
  - Are consistent, accurate and equitable across all involved parties
  - Are ethically and responsibly managed and effectively communicated to the interventional cardiology community

- Details of the Communications Plan were issued by email on August 19

CONFIDENTIALITY

Terms of Confidentiality

DAPT STUDY

- As outlined in the confidentiality agreements:
  - All study results are strictly confidential and shall not be disclosed even internally within your organizations
  - The manuscripts are expected to be circulated for review on or around September 18, 2014, at which time up to 3 additional non-marketing individuals may sign CDAs and be allowed to review the study results, for purposes of assessing the publications.
  - Use of study results is restricted for internal evaluation only. They cannot be used in any way relating to marketing of the device or drug.
  - Terms of confidentiality are in force until the publication date, expected to be November 16, 2014

DAPT STUDY

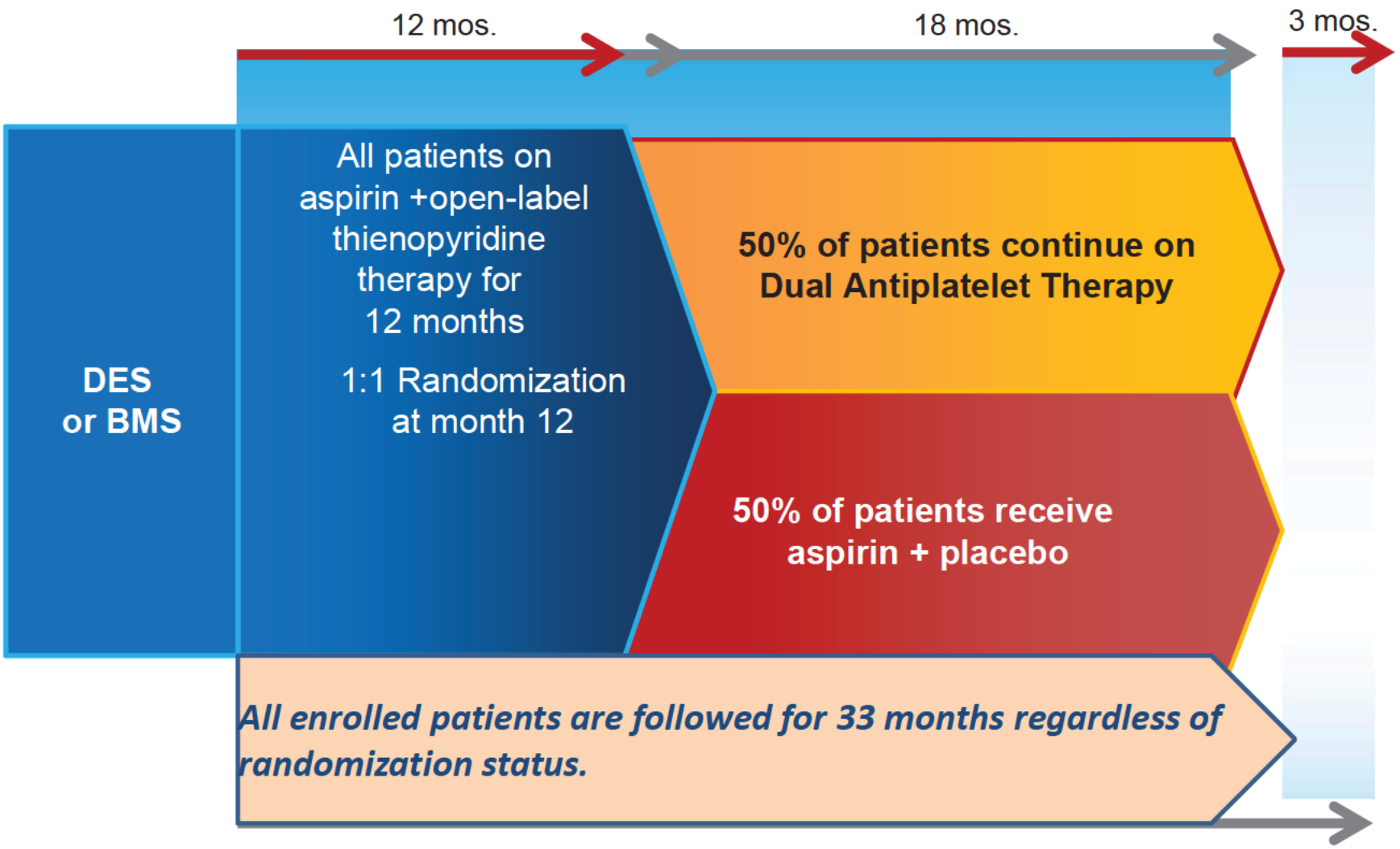
Primary Endpoint Results: DES

Objectives

The DAPT Study was designed as a multicenter, international randomized placebo-controlled trial to compare 30 versus 12 months of dual antiplatelet therapy in a broadly inclusive subject population treated with coronary stents with the objectives of:

- Determining whether dual antiplatelet therapy beyond 12 months is associated with reduction in MACCE (death, myocardial infarction or stroke) and/or stent thrombosis
- Determining the impact of dual antiplatelet therapy beyond 12 months on major bleeding

Design



Total 33 month patient evaluation including additional 3-month follow-up off study drug

Mauri, Kereiakes et al AHJ 2010; 160(6): 1035-1041

ClinicalTrials.gov number NCT00977938

Design

DAPT STUDY

Primary analysis of DES-treated subjects, randomized to 12 vs. 30 months of dual antiplatelet therapy

- Operator selection of stent and thienopyridine type from those approved by FDA at enrollment
- Site enrollment by HCRI or from 1 of 4 stent-manufacturer sponsored studies – each with uniform randomization criteria, end point definition, and follow-up as specified by overall DAPT Study
- Randomization stratified according to site, thienopyridine drug type, and by presence of risk factors for stent thrombosis
- All potential endpoint events adjudicated by one CEC, blinded to treatment
- Safety monitored by an independent overall DSMB
- No formal interim efficacy analysis was specified to stop the study or adapt the design

Mauri, Kereiakes et al AHJ 2010; 160(6): 1038-1041

Study Endpoints

Two powered co-primary effectiveness endpoints

- Academic Research Consortium (ARC) definite/probable stent thrombosis (ST) at 12-30 months post-procedure
- MACCE (death, MI or stroke) at 12-30 months post-procedure

Powered primary safety endpoint

- Major bleeding, defined as “moderate” or “severe” by Global Utilization of Streptokinase and TPA for Occluded Arteries (GUSTO) classification at 12-30 months post-procedure

Co-Primary Effectiveness Hypotheses

DAPT STUDY

30m DAPT increases survival free from MACCE (vs. 12m DAPT) over the 12-30m period after stent treatment:

H_o: $\lambda_{12m\text{-}DAPT} = \lambda_{30m\text{-}DAPT}$

H_A: $\lambda_{12m\text{-}DAPT} \neq \lambda_{30m\text{-}DAPT}$

where λ is hazard rate of MACCE over12-30m period.

30m DAPT increases survival free from ST (vs. 12m DAPT) over the 12-30m period after stent treatment:

H_o: $\gamma_{12m\text{-}DAPT} = \gamma_{30m\text{-}DAPT}$

H_A: $\gamma_{12m\text{-}DAPT} \neq \gamma_{30m\text{-}DAPT}$

where γ is hazard rate of stent thrombosis over 12-30m period

Use of Benjamini-Hochberg approach to control multiple comparisons:

(1) p<0.05 on both endpoints and HRs favor 30 m DAPT => 30m DAPT superior to 12m DAPT on both; IF NOT

(2) p<0.025 on one endpoint and HR favors 30m DAPT => 30m DAPT superior to 12m DAPT on that endpoint

Primary Safety Hypothesis

DAPT STUDY

Non-inferiority: 30m DAPT is associated with major bleeding rates at 12-30m post-stenting that does not exceed that of control arm by δ = 0.008 (0.8%) or more:

$$H_o: \pi_{30m\text{-}DAPT} \geq \pi_{12m\text{-}DAPT} + \delta$$

$$H_A: \pi_{30m\text{-}DAPT} < \pi_{12m\text{-}DAPT} + \delta$$

where π30m-DAPT is true major bleed rate for 30m DAPT arm and π12m-DAPT is true major bleed rate for control arm

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Partnership, Sponsorship and Funding

- Public-private partnership involving:
  - US FDA
  - Harvard Clinical Research Institute (HCRI, Boston, MA) as the study sponsor
  - 8 funding stent and pharmaceutical manufacturers
    - Abbott Vascular
    - Boston Scientific Corp.
    - Bristol-Myers Squibb Co./Sanofi Pharmaceuticals Partnership
    - Cordis Corp.
    - Daiichi Sankyo Co. Limited
    - Eli Lilly & Co.
    - Medtronic Vascular
  - With additional funding provided by grant from US DHHS (1RO1FD003870-01)

Study Administration

DAPT STUDY

Co-Principal Investigators

Laura Mauri, Dean Kereiakes

Study Statistician

Joseph Massaro

Executive Committee

Laura Mauri, Dean Kereiakes, Donald Cutlip, Sharon-Lise Normand, P. Gabriel Steg, Robert Yeh, Theodora Cohen, Priscilla Driscoll-Shempp

Advisory Committee

Eugene Braunwald (Chair), Ralph Brindis, David Cohen, Anthony Gershlick, Paul Gurbel, David Holmes, Alice Jacobs, Michael Linkoff, Daniel Simon, Jean-François Tanguay, Douglas Weaver, Stephan Windecker, Steve Wiviott

Data Monitoring Committee

Robert Bonow (Chair), Charles Davidson, James Neaton, William Wijns, Eric Bates, Clyde Yancy (ex officio)

Clinical Events Committee

Donald E. Cutlip

National Coordinating Investigators

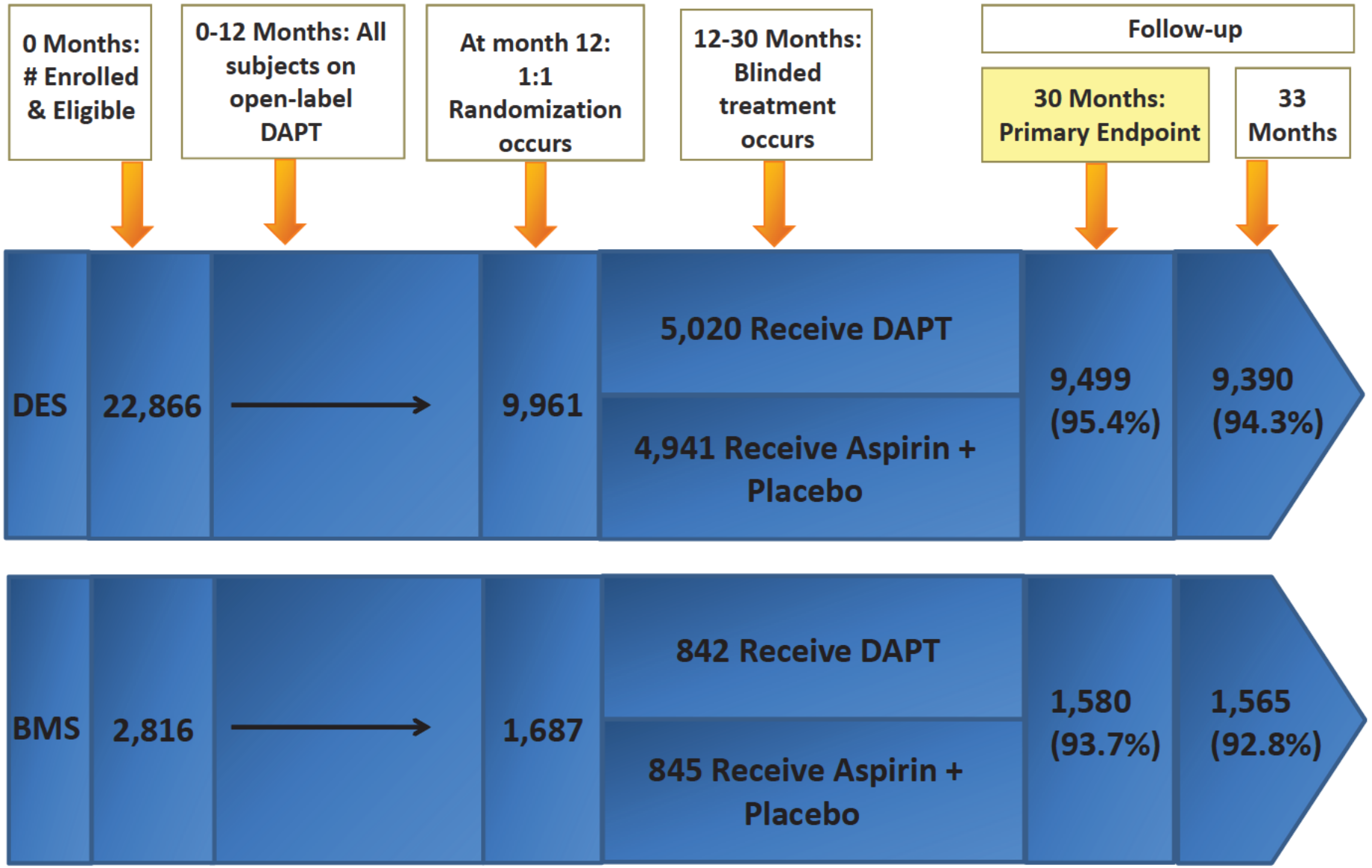
P. Gabriel Steg (France), Ian Meredith (Australia), John Ormiston (New Zealand), Harold Darius (Germany), Anthony Gershlick (United Kingdom), Wojciech Wrobel (Poland), Laura Mauri & Dean Kereiakes (United States)

Enrolling Sites

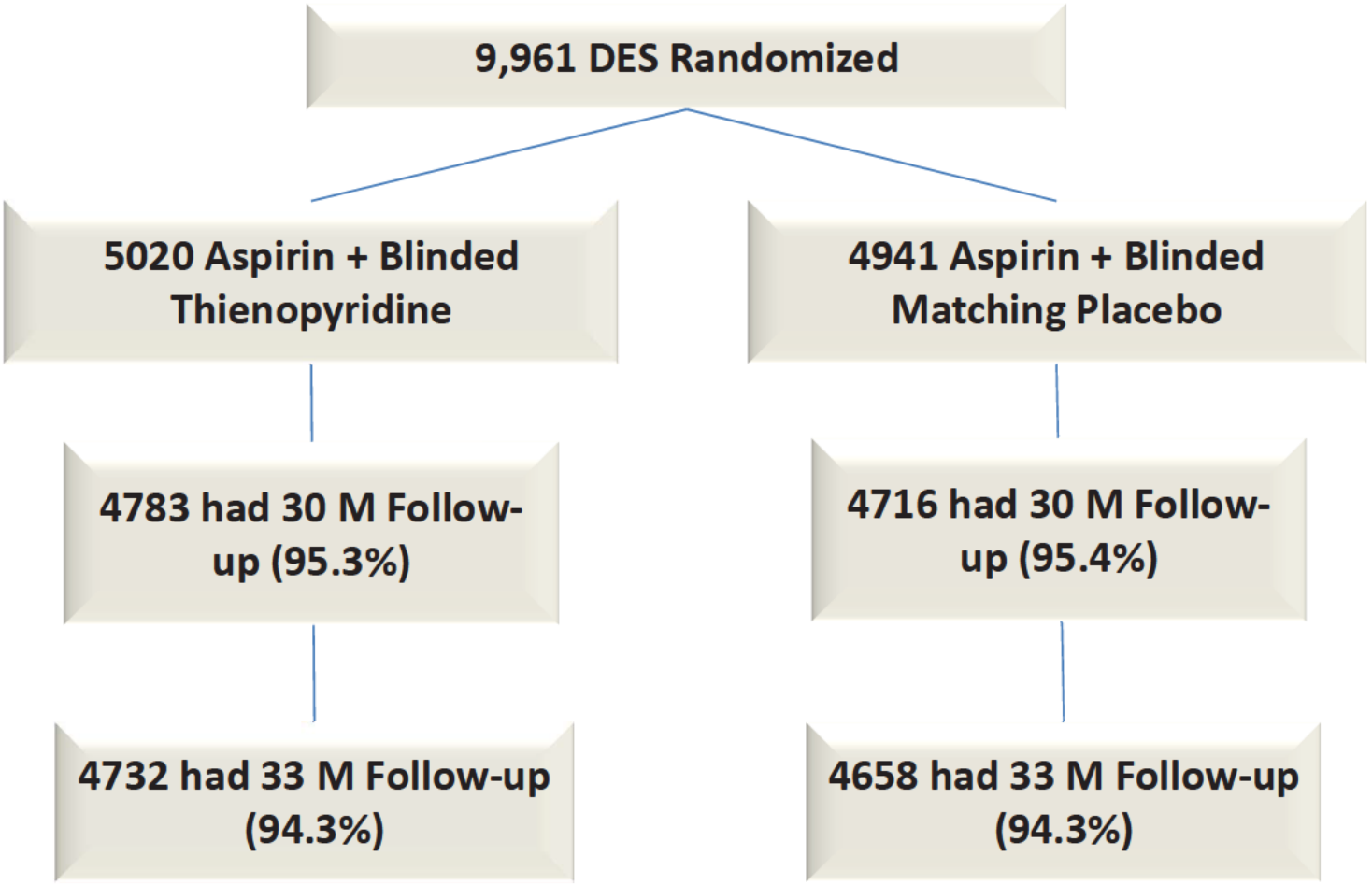
DAPT STUDY

452 Sites in 11 Countries

Subject Flow



Subject Flow: Randomized DES



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Baseline Demographics
DES ITT

DAPT STUDY

	30 Month DAPT N=5020	12 Month DAPT N=4941	P-value
Age (years)	61.8	61.6	0.24
Female	24.7%	26.0%	0.15
Race – Non White	8.9%	8.6%	0.69
Ethnicity-Hispanic or Latino	3.2%	3.3%	0.91
Weight – kg	91.5	91.5	0.93
BMI	30.5	30.6	0.92
Diabetes Mellitus	31.1%	30.1%	0.28
Hypertension	75.8%	74.0%	0.03
Cigarette Smoker	24.6%	24.7%	0.91
Prior PCI	30.4%	31.0%	0.50
Prior CABG	11.3%	11.8%	0.49
NSTEMI	15.5%	15.5%	0.93
STEMI	10.6%	10.3%	0.65

ST Risk Factors at Index Procedure, DES ITT

DAPT STUDY

	30 Month DAPT N=5020	12 Month DAPT N=4941	P-value
ACS (NSTEMI or STEMI)	26.1%	25.9%	0.80
Renal insufficiency/failure	4.5%	4.0%	0.27
LVEF < 30%	1.7%	1.5%	0.40
> 2 vessels stented	0.4%	0.6%	0.15
> 2 lesions per vessel	1.9%	1.9%	0.88
Lesion length ≥ 30 mm	10.0%	10.2%	0.87
Bifurcation lesion	6.5%	6.5%	0.97
ISR of DES	3.1%	3.2%	0.86
Vein bypass graft	2.5%	3.1%	0.09
Unprotected left main	0.4%	0.5%	0.54
Thrombus-containing lesion	11.8%	11.7%	0.87
Prior brachytherapy	0.3%	0.3%	1.00
Any Risk Factor	50.7%	51.0%	0.81

Lesion and Procedure Characteristics, DES ITT

DAPT STUDY

	30 Month DAPT N=5020 (6594 Lesions)	12 Month DAPT N=4941 (6413 Lesions)	P-Value
Number of Treated Vessels (per subject)	1.1	1.1	0.60
Number of Stents (per subject)	1.5	1.5	0.23
Minimum Stent Diameter (mm, per subject)	2.9	2.9	0.86
Total Stent Length (mm, per patient)	27.7	27.4	0.43
Native Coronary	97.1%	96.8%	0.36
Left Main	0.8%	0.9%	0.92
LAD	41.2%	40.4%	0.33
Circumflex	22.4%	23.5%	0.12
RCA	32.7%	32.1%	0.49
Venous Graft	2.34%	2.70%	0.20
Arterial Graft	0.55%	0.47%	0.54
Modified ACC/AHA Lesion Class B2 or C	43.5%	43.1%	0.65

Study Update

CONFIDENTIAL

17 September 2014

Agenda

1. Review of DES 30 vs 12m primary results
2. Update on DES vs BMS propensity analysis, and BMS 30 vs 12m RCT results
3. Update on NCVD analyses and case review plan
4. Update regarding inquiry from CDER regarding early safety release
5. DMC meeting Sept 9, 2014
6. FDA Comments
7. Manufacturer Comments
8. Communication Strategy and Timeline

Attendees

Study Leadership: Laura Mauri, MD, *PI,* Dean Kereiakes, MD, *co-PI*

HCRI: Priscilla Driscoll Shempp, *DAPT Study Project Director*

FDA

- **CRDH**:
  - Andy Farb, MD, *Senior Medical Reviewer, Division of Cardiovascular Devices*
  - Bram Zuckerman, MD, *Director, Division of Cardiovascular Devices*
- **CDER**:
  - Mary Ross Southworth, PharmD, *Deputy Director, Safety, Division of Cardiovascular and Renal Prod*
  - Karen Hicks, MD, *Medical Officer, Division of Cardiovascular and Renal Prod*
  - Bob Temple, MD, *Deputy Director for Clinical Science*
  - Ellis Unger, MD, *Director, Office of Drug Evaluation I/Office of New Drugs*

Device Manufacturers

- **Abbott**: Charles Simonton, MD, *Chief Medical Officer, Divisional VP, Med. Affairs*
- **Boston Scientific**: Keith Dawkins, MD, *Global Chief Medical Officer*
- **Cordis**: Patti Schleckser, *Director of Clinical Research*
- **Medtronic**: Sandeep Brar, MD, *Director of Clinical Research*

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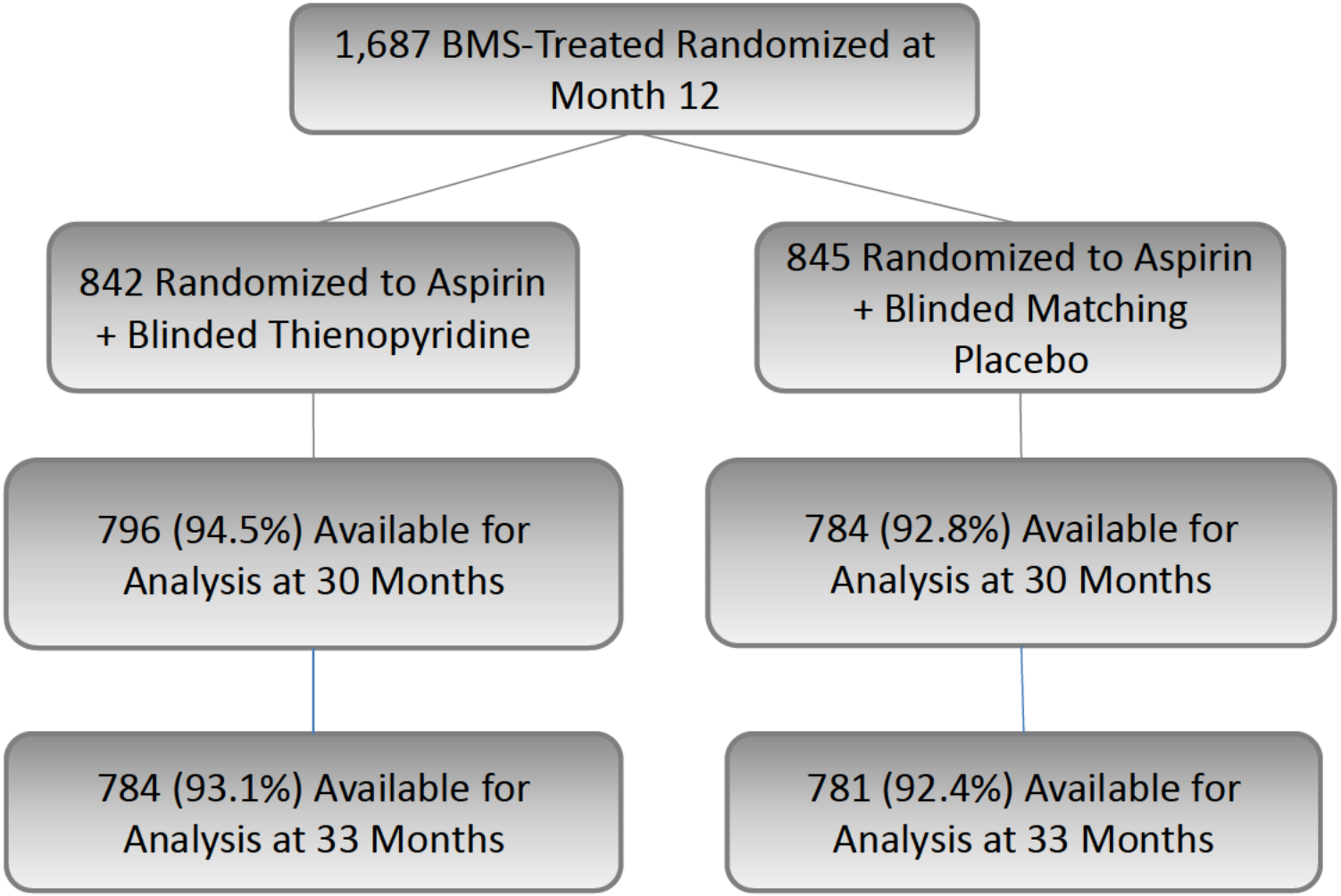
Pharmaceutical Manufacturers

- **Bristol-Myers Squibb**: Charlotte Jones-Burton, MD, *Director, CV Medical Strategy*
- **Daiichi Sankyo**: Dmitry Zamoryakhin MD, *Director, Cardiovascular Clinical Development*
- **Eli Lilly**: LeRoy LeNarz, MD, *Sr. Medical Director – Cardiovascular*
- **Sanofi**: William Daley, MD, *VP of Business Development & Licensing*

MacDougall Biomedical Communications: Kari Watson, *Senior Vice President*

BMS ITT 12 VS. 30 MONTH ANALYSIS

Subject Flow: Randomized BMS



Primary Effectiveness Outcomes, BMS ITT, 12-30 Months F/U

DAPT STUDY

Outcome	30 Month DAPT N=842	12 Month DAPT N=845	Stratified HR, 95% CI	Stratified Log-rank P-Value
Stent Thrombosis ARC Definite/Probable	**4 (0.5%)**	**9 (1.1%)**	**0.49 (0.15-1.64)**	**0.24**
ARC Definite	4 (0.5%)	9 (1.1%)	0.49 (0.15-1.64)	0.24
ARC Probable	0 (0.0%)	0 (0.0%)	-- (--, --)	
MACCE (Death, MI, Stroke)	**33 (4.0%)**	**38 (4.7%)**	**0.92 (0.57-1.47)**	**0.72**
Death	8 (1.0%)	10 (1.2%)	0.90 (0.35-2.33)	0.83
Cardiac	4 (0.5%)	5 (0.6%)	1.03 (0.26-4.12)	0.97
Vascular	0 (0.0%)	0 (0.0%)	-- (--, --)	
Non-Cardiovascular	4 (0.5%)	5 (0.6%)	0.79 (0.21-2.96)	0.73
MI	22 (2.7%)	25 (3.1%)	0.91 (0.51-1.62)	0.74
Stroke (total)	6 (0.7%)	5 (0.6%)	1.22 (0.37-4.01)	0.74
Ischemic stroke	4 (0.5%)	5 (0.6%)	0.82 (0.22-3.05)	0.77
Hemorrhagic stroke	1 (0.1%)	0 (0.0%)	-- (--, --)	0.32
Type Uncertain	1 (0.1%)	0 (0.0%)	-- (--, --)	0.32

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ACS for ST and MACCE, BMS ITT; 12-30 Months F/U

	30 Month DAPT N (%)	12 Month DAPT N (%)	HR (95% CI)	P Value for Interaction
ARC Definite/Probable ST				
No ACS Within 72 Hours	2 (0.6%)	1 (0.3%)	2.04 (0.18-22.47)	0.14
ACS Within 72 Hours	2 (0.4%)	8 (1.7%)	0.24 (0.05-1.14)	
MACCE				
No ACS Within 72 Hours	17 (5.0%)	17 (5.0%)	1.02 (0.52-2.00)	0.50
ACS Within 72 Hours	16 (3.3%)	21 (4.5%)	0.74 (0.39-1.42)	

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DAPT STUDY

Study Update

24 October 2014

Agenda

1. Brief Review of Primary Results
2. Adjudication Analysis Results
3. Meta-analysis of Published Data
4. Communication Plan
5. Questions and Discussion

Attendees

Study Leadership: Laura Mauri, MD, *PI,* Dean Kereiakes, MD, *co-PI*

HCRI: Priscilla Driscoll Shempp, *DAPT Study Project Director*

- **MacDougall Biomedical Communications**: Kari Watson, *Senior Vice President*
- **CardioMed:** Semih Oktay, *President*

FDA

- **CDRH**:
  - Andy Farb, MD, *Medical Officer, Division of Cardiovascular Devices*
  - Bram Zuckerman, MD, *Director, Division of Cardiovascular Devices*
- **CDER**:
  - Mary Ross Southworth, PharmD, *Deputy Director, Safety, Division of Cardiovascular and Renal Prod*
  - Karen Hicks, MD, *Medical Officer, Division of Cardiovascular and Renal Prod*
  - Norman Stockbridge, MD, PhD, Director, Division of Cardiovascular and Renal Products
  - Robert Temple, MD, *Deputy Director for Clinical Science (tentative)*
  - Douglas Throckmorton, *MD, Deputy Director of the Center for Drug Evaluation and Research*

Device Manufacturers

- **Abbott**: Gary Johnson, *Divisional VP, Global Clinical, Regulatory & HEOR*
- **Boston Scientific**: Keith Dawkins, MD, *Global Chief Medical Officer and Executive Vice President*
- **Cordis**: Patti Schleckser, *Director of Clinical Research*
- **Medtronic**: Sidney Cohen, MD, PhD, *Medical Advisor, Clinical Affairs*

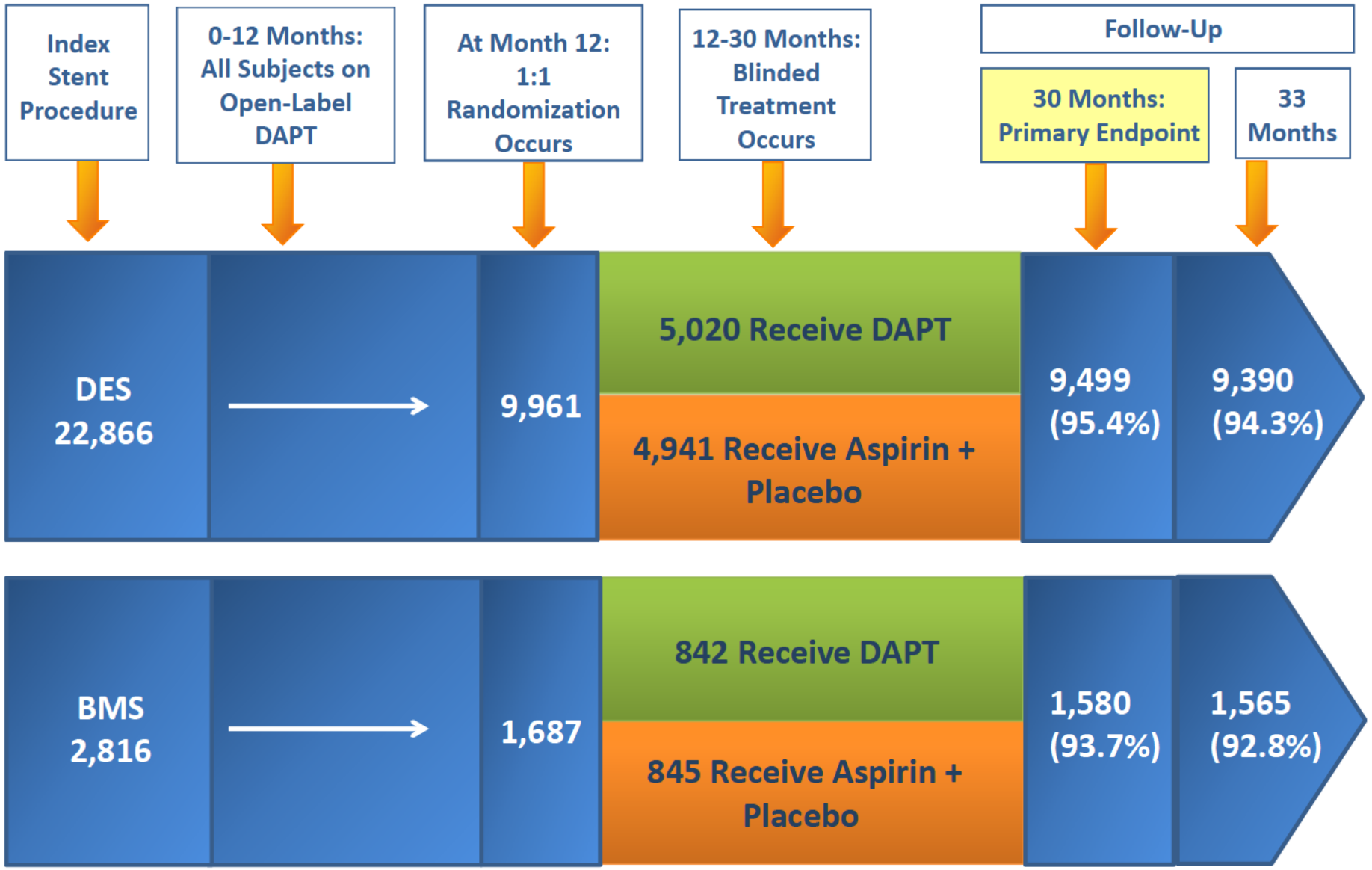
Pharmaceutical Manufacturers

- **Bristol-Myers Squibb:** Charlotte Jones-Burton, MD, *Director, CV Medical Strategy*
- **Daiichi Sankyo**: Dmitry Zamoryakhin, MD, *Director, Cardiovascular Clinical Development*
- **Eli Lilly**: LeRoy LeNarz, MD, *Sr. Medical Director – Cardiovascular*
- **Sanofi**: William Daley, MD, *VP of Business Development & Licensing (on behalf of Sanofi/BMS JV)*

DAPT STUDY

Summary of Primary Results

Subject Flow: All



Co-Primary Effectiveness Endpoints & Components, BMS ITT: 12-30 Months F/U

DAPT STUDY

Outcome	Thienopyridine N=842	Placebo N=845	Stratified HR, 95% CI	Stratified Log-rank P-Value
Stent Thrombosis ARC Definite/Probable	**4 (0.5%)**	**9 (1.1%)**	**0.49 (0.15-1.64)**	**0.24**
ARC Definite	**4 (0.5%)**	**9 (1.1%)**	**0.49 (0.15-1.64)**	0.24
ARC Probable	0 (0.0%)	0 (0.0%)	-- (--, --)	
MACCE (Death, MI, Stroke)	33 (4.0%)	38 (4.7%)	0.92 (0.57-1.47)	0.72
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MI	22 (2.7%)	25 (3.1%)	0.91 (0.51-1.62)	0.74
Stroke (total)	6 (0.7%)	5 (0.6%)	1.22 (0.37-4.01)	0.74
Ischemic stroke	4 (0.5%)	5 (0.6%)	0.82 (0.22-3.05)	0.77
Hemorrhagic stroke	1 (0.1%)	0 (0.0%)	-- (--, --)	0.32
Type Uncertain	1 (0.1%)	0 (0.0%)	-- (--, --)	0.32

DAPT
STUDY

Questions and Discussion

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/s/

THOMAS A MARCINIAK
12/12/2014

CLINICAL REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: March 7, 2013

Reviewer: Thomas A. Marciniak, M.D.
Medical Team Leader

TSI: 935

Drugs: Angiotensin receptor blockers (ARBs)

Subject: Risk of cancer

Summary

BACKGROUND: A published meta-analysis raised the question of whether use of angiotensin receptor blockers (ARBs) is associated with an increased risk of cancer.

METHODS: To identify all malignancy adverse events I followed a pre-specified analysis plan to analyze the raw data from all 16 large ARB clinical outcomes trials submitted to the FDA. Using the malignancy determinations I performed pre-specified patient-level meta-analyses of incidences of lung, prostate, and hematologic malignancy events and Kaplan-Meier analyses and Cox regressions (stratified by trial and including baseline cofactors) of incidence rates and of survival after malignancy diagnosis.

RESULTS: I excluded five trials from the primary analyses because they failed the pre-specified criteria for completeness of follow-up and malignancy reporting. The pooled risk ratio for lung cancer comparing the ARB arms to the control arms in the 11 trials with adequate data was 1.24 (95% confidence interval 1.08-1.43, p = 0.003). The increased risk of lung cancer with ARBs was robust to meta-analyses excluding the index trial, including all four of the excluded trials that had malignancy site reporting, and analyzing new diagnoses alone. Kaplan-Meier analyses estimated about 0.8 excess lung cancer cases per year per 1,000 patients treated. Cox regressions estimated about a 4-fold higher risk in ex-smokers and an 11-fold higher risk in current smokers

compared to non-smokers regardless of ARB use. Survival after a lung cancer event was dismal, about 34 percent at one year regardless of initial ARB use. The meta-analyses for prostate and hematologic malignancies were inconclusive. Solid cancer rates (excluding non-melanoma skin cancers and brain tumors) were slightly but not significantly increased with ARB use.

CONCLUSION: ARB use is associated with an increased risk of lung cancer.

Introduction

In 2010 a meta-analysis published by Sipahi *et al.* raised the question of whether use of angiotensin receptor blockers (ARBs) is associated with an increased risk of cancer. (Sipahi, Debanne et al. 2010) Sipahi *et al.* analyzed cancer data from publications and from the FDA website for 61,590 patients from five trials and observed that patients randomized to ARBs had a significantly increased risk of new cancers (risk ratio (RR) 1.08, 95% confidence interval (CI) 1.01-1.15). They also analyzed specific solid cancer sites and found that only new lung cancers were significantly more frequent in the ARB arms (RR 1.25, 95% CI 1.05-1.49). They concluded that their findings warranted further investigation.

The Sipahi *et al.* meta-analysis stimulated other meta-analyses and observational studies addressing similar issues. Bangalore *et al.* analyzed 70 antihypertensive trials with 324,168 patients. (Bangalore, Kumar et al. 2011) Regarding ARBs they found no difference in cancer risk, although they observed an increased cancer risk with the combination of ARBs with angiotensin converting enzyme inhibitors (ACEI) by a fixed effect meta-analysis but not by a random effects one. The ARB Trialists Collaboration analyzed 15 ARB trials with 138,769 patients and found no excess cancer risk with ARB use. (ARB Trialists Collaboration 2011) The FDA conducted a trial-level meta-analysis of 31 trials and approximately 156,000 patients and concluded that ARB treatment does not increase the risk of cancer. (FDA 2011)

All of the published meta-analyses have severe limitations regarding trials included and the information available on cancer cases in publically available trial data. For example, regarding trials included, the ARB Trialists Collaboration analyzed only the LIFE trial for losartan, omitting three other major losartan trials because they were not able to obtain the data. Regarding information on cancer cases, Bangalore *et al.* counted seven cancer cases for the losartan RENAAL trial and referenced the main RENAAL publication. (Brenner, Cooper et al. 2001) However the main RENAAL publication does not include statistics on cancer cases. I queried the meta-analysis authors and they confirmed that they had obtained the RENAAL cancer incidences from a 2008 meta-analysis. (Coleman, Baker et al. 2008) The latter meta-analysis also referenced only the main RENAAL publication. Upon query the author of the 2008 meta-analysis quoted the source as a RENAAL substudy publication. (Remuzzi, Ruggenenti et al. 2004) However, the RENAAL substudy publication tabulated cancer cases only for adverse events leading to patient withdrawal. Because cancer is not a reason for withdrawing ARB

treatment, counting only withdrawals grossly underestimates cancer incidence (as confirmed by the RENAAL data submission to the FDA.)

The FDA meta-analysis did not correct the flaws present in the meta-analyses using published data. The FDA requested summary trial data from the drug companies but did not specify details on how to classify incident cases, ambiguous cases, or censoring periods and did not mandate submission of data for all relevant trials. Furthermore, the FDA meta-analysis of lung cancers was seriously flawed in that it did not count lung carcinomas as lung cancers but was inappropriately limited to lung cancers coded as "malignant lung neoplasm".

Sipahi was unaware of these flaws in the FDA meta-analysis but publically criticized it for not exploring exposure-risk relationships in a patient-level analysis. (Wood 2011) I agree with Sipahi that as serious a question as whether widely-used antihypertensives increase cancer risk deserves the most discriminating analysis possible. I proceeded with a patient-level meta-analysis of the raw data in long-term ARB trials submitted to the FDA as recommended in an editorial on the Sipahi *et al.* meta-analysis. (Nissen 2010)

My experience with ARBs and cancer predates the Sipahi *et al.* meta-analysis: I had performed the primary clinical review of the losartan LIFE trial submitted to the FDA in 2002. (Marciniak 2003) I observed then that there was a numeric but not statistically significant excess of lung cancers in the losartan arm in that trial. I also observed that there was a less prominent numeric excess of prostate cancers in the losartan arm. Re-examining the LIFE data after the publication of the Sipahi *et al.* meta-analysis I observed additionally that hematologic malignancies were less frequent in the losartan arm. I hypothesized that the latter result, if real, might be related to the same mechanism responsible for the slight suppression of hematopoiesis observed with both ARBs and ACEIs. (Leshem-Rubinow, Steinvil et al. 2012) I hypothesized also that the excess of prostate cancers, if real, might be related to an increase in adrenal androgen levels resulting from the same mechanism responsible for aldosterone breakthrough following chronic ARB or ACEI use. (Bomback and Klemmer 2007)

Hence I targeted the following three independent hypotheses in patient-level meta-analyses:

1. That ARB use increases the risk of lung cancer. Because I had no *a priori* hypothesis that ACEIs share this effect, I pre-specified for the primary analysis of lung cancers ignoring the use of ACEIs both as controls and in the ARB arms.

2. That ARB use increases the risk of prostate cancer. For this hypothesis I pre-specified criteria for eliminating trials only with ACEI control arms or with substantial use of ACEIs during the trial. Because of resource limitations, i.e., I performed this work without official FDA support, I did not analyze the data by concomitant ACEI use in the ARB arms.

3. That ARB use decreases the risk of hematologic malignancies. Regarding ACEI use I proposed analyzing this hypothesis identically to that regarding prostate cancer.

Because previous meta-analyses had also targeted all cancers, I also analyzed all solid cancers excluding non-melanoma skin cancers and brain tumors. I excluded hematologic malignancies because I hypothesize that ARBs may decrease them, non-melanoma skin cancers because of their less serious nature compared to other solid cancers and because they are under-reported, and brain tumors because their malignancy status is frequently not reported and because most ARBs do not cross the blood-brain barrier.

Methods

Trial Selection

I adopted the same general criteria for trial size and duration used by the Sipahi *et al.* and FDA meta-analyses: randomized, placebo-and active comparator-controlled studies for the ARBs; enrolled more than 100 patients; had a mean or median follow-up longer than one year; and collected cancer data either as a prespecified endpoint or adverse event. I considered only trials for which the sponsors had submitted complete data (i.e., protocols, case report forms, and datasets) to the FDA.

Regarding trial data I looked for data on all cancer-related events, not just deaths, and for data on the primary site of the cancer, because the hypotheses involve specific sites and not all cancers. I prespecified excluding trials from the primary analyses if more than five percent of all cancers were detected only at study end or death or if the primary sites were not reported for more than five percent of the cancers (other than cancers reported explicitly as unknown primaries). Because I have concerns about the validity of any results from trials having poor follow-up and I have documented serious problems with them in previous reviews, I prespecified excluding trials from the primary analyses if completeness of follow-was less than 90 percent. For the hypotheses regarding prostate cancer and hematologic malignancies, which postulate similar effects for both ARBs and ACEIs, I prespecified excluding trials from the primary analyses if the trials had only ACEI control arms or if the concomitant use of ACEIs in the trials exceeded 10 percent.

Consulting with other FDA staff I identified 16 ARB trials with data submitted to the FDA and meeting the general criteria for trial size and duration. I excluded five of these 16 trials from the primary analyses because of incomplete follow-up or incomplete cancer ascertainment (see Appendix 1) and included 11 trials in the meta-analysis of lung cancer. I excluded six of the 11 trials from the meta-analyses of prostate and hematologic malignancies because of ACEI use. I list the trials used in the primary meta-analyses in Table 1 and those excluded in Table 2**.**

Table 1: Trials Included in the Primary Meta-Analyses

ARB	Trial	Reference	NDA	N	Prostate/heme analyses?
candesartan	Charm-Added	(McMurray, Ostergren et al. 2003)	20838 S022	2548	No, ACEI use ~100%
	Charm-Alternative	(Granger, McMurray et al. 2003)	20838 S022	2028	Yes
	Charm-Preserved	(Yusuf, Pfeffer et al. 2003)	20838 S022	3023	No, ACEI use ~20%
irbesartan	(b) (4)				
	IDNT	(Lewis, Hunsicker et al. 2001)	20757 S021	1716	Yes
losartan	LIFE	(Dahlof, Devereux et al. 2002)	20386 S032	9193	Yes
	RENAAL	(Brenner, Cooper et al. 2001)	20386 S028	1513	Yes
telmisartan	ONTARGET	(Yusuf, Teo et al. 2008)	20850 S025	25620	No, ACEI control arm
	PRoFESS	(Yusuf, Diener et al. 2008)	20850 S025	20332	No, ACEI use ~31%
	TRANSCEND	(Yusuf, Teo et al. 2008)	20850 S025	5926	Yes
valsartan	Val-Heft	(Cohn and Tognoni 2001)	20665 S016	5010	No, ACEI use ~93%

Table 2: Trials Excluded from the Primary Meta-Analyses

ARB	Trial	Reference	IND/NDA	N	Reason Excluded
irbesartan	IRMA 2	(Parving, Lehnert et al. 2001)	N20757 S021	611	Incomplete follow-up
olmesartan	(b) (4)				
valsartan					
	VALIANT	(Pfeffer, McMurray et al. 2003)	N21283 S011	14679	Incomplete cancer reporting

The 11 trials for the lung cancer meta-analysis include 85,925 patients and studied five different ARBs while the five trials for the prostate and hematologic malignancies meta-analyses include 20,376 patients and studied four ARBs. The five excluded trials total 29,832 patients and studied three ARBs. Two FDA-approved ARBs, azilsartan and eprosartan, did not have any eligible trials submitted to the FDA. The FDA approved azilsartan in 2011 and its sponsor has not conducted large outcome trials with it. (b) (4) The other FDA-approved ARB not included in the primary meta-analyses, olmesartan, had two trials with FDA data submissions meeting the general criteria but failing the criterion for completeness of follow-up.

Cancer Ascertainment

From the study protocols, case report forms (CRFs), and dataset documentation I identified all CRFs and datasets having data regarding cancers. The CRFs having cancer data included adverse event forms, serious adverse event forms, endpoint forms, procedure forms, end of treatment forms, disposition forms, and death forms depending upon the particular study. I used computer string searches to identify possible cancer cases from the investigator-reported verbatim terms in the corresponding datasets and string matches to standard cancer terms if coded terms were available. The string searches included misspellings and ambiguous terms, (e.g., "kancer", "lung mass") and I designed them to be sensitive rather than specific. Blinded to treatment assignment I manually reviewed all possible cancer cases, consulting primarily the investigator-reported verbatim terms and comments but reviewing the full case report forms for ambiguous cases. I assigned a primary cancer site, e.g., "lung", "prostate", if the case had adequate documentation of malignancy or seriousness and of the primary site. If medical histories included cancer sites I assigned cancer sites using the same approach.

For the post-randomization cancer events I assigned a date of first clinical diagnosis of the cancer or cancer recurrence. I used date of first clinical diagnosis because date of histologic diagnosis is frequently not available in trial CRFs. I identified both initial diagnoses of cancers, i.e., incident new cancers, as well as recurrences of cancers originally diagnosed prior to randomization, distinguishing the new cancers when possible. I consider cancer recurrences to be as clinically relevant as incident new cancers because cancer patients die more frequently from the local or metastatic recurrence than from the original primary.

Finally, I identified for each trial the earliest last follow-up date, e.g., the global study end date or the primary endpoint censoring date. I counted cancer events by the intent-to-treat (ITT) principle if they occurred on or after the randomization date and before or on the earliest last follow-up date. I did not attempt to censor the cancers occurring shortly after randomization despite the realization that they are highly unlikely to be related to study drug use; I do not have an *a priori* justification for a censoring date and, being infrequent, counting them does not appear to affect substantially the meta-analyses. I relied upon the incidence curves to show any differences in early vs. later rates. I favor and pre-specified the ITT approach because it is the only approach that preserves the randomization and, if the effect size is less than two-fold, the majority of cancers will be numerically unrelated to the study drug use. Furthermore, cancers frequently require weeks to diagnose but cause adverse effects leading earlier to study drug discontinuation. I would consider an on-treatment analysis allowing an adequate time for delayed diagnoses as a sensitivity analysis but, because of resource limitations, I did not assign dates of last treatment and perform on-treatment analyses.

Statistical Analysis

I performed all statistical analyses using Stata 12. For the meta-analyses I used the *metan* package. (Harris, Bradburn et al. 2008) Because I hypothesized similar effects for all ARBs, I performed fixed-effect meta-analyses of risk ratios evaluated by the Mantel-Haenszel method. I evaluated heterogeneity with the I^2 statistic.

To show the time course of cancer development I generated Kaplan-Meier plots of time to first cancer event occurrences. I also generated Kaplan-Meir plots of survival after first clinical diagnosis of a new or recurrent cancer. I used crude survival rather than cause-specific survival, i.e., deaths due to cancer, because I believe that cancer usually contributes to the demise of patients with recurrent or metastatic cancer. I estimated statistical significance of the time courses of cancer development and survival following cancer diagnosis by log rank tests stratified by study. I explored the effects of baseline factors by Cox regressions stratified by study. For the Cox regressions I tested the proportional hazards assumptions by graphs and statistics of Schoenfeld residuals produced by the Stata 12 *estat phtest* command.

Results

Lung Cancer

I identified new or recurrent lung cancer events during the censoring periods in 805 of the 85,925 patients in the eleven trials. The pooled RR comparing the ARB arms to the control arms is 1.24 (95% CI 1.08-1.43, p = 0.003). I show the forest plot of RRs by trial in Figure 1. The I^2 statistic did not suggest significant heterogeneity (p > 0.6). All of the trials except one, CHARM-Preserved, showed an excess of lung cancers in the ARB arms. The CI for the CHARM-Preserved risk ratio overlaps with the risk ratio CIs for all eleven trials and for the ten trials excluding CHARM-Preserved. Because LIFE was the index study suggesting an effect of an ARB upon lung cancer, I performed a second meta-analysis excluding LIFE. The pooled RR excluding LIFE is also 1.24 (95% CI 1.07-1.44, p = 0.005). As sensitivity analyses I performed meta-analyses including the trials excluded from the primary analyses. For a meta-analysis including the one irbesartan study excluded (IRMA 2), the pooled RR remains 1.24 and the p value is 0.003. For a meta-analysis including all 15 trials that collected the cancer sites for all malignancies, i.e., all except VALIANT, the pooled RR is 1.16 and the p value is 0.026.

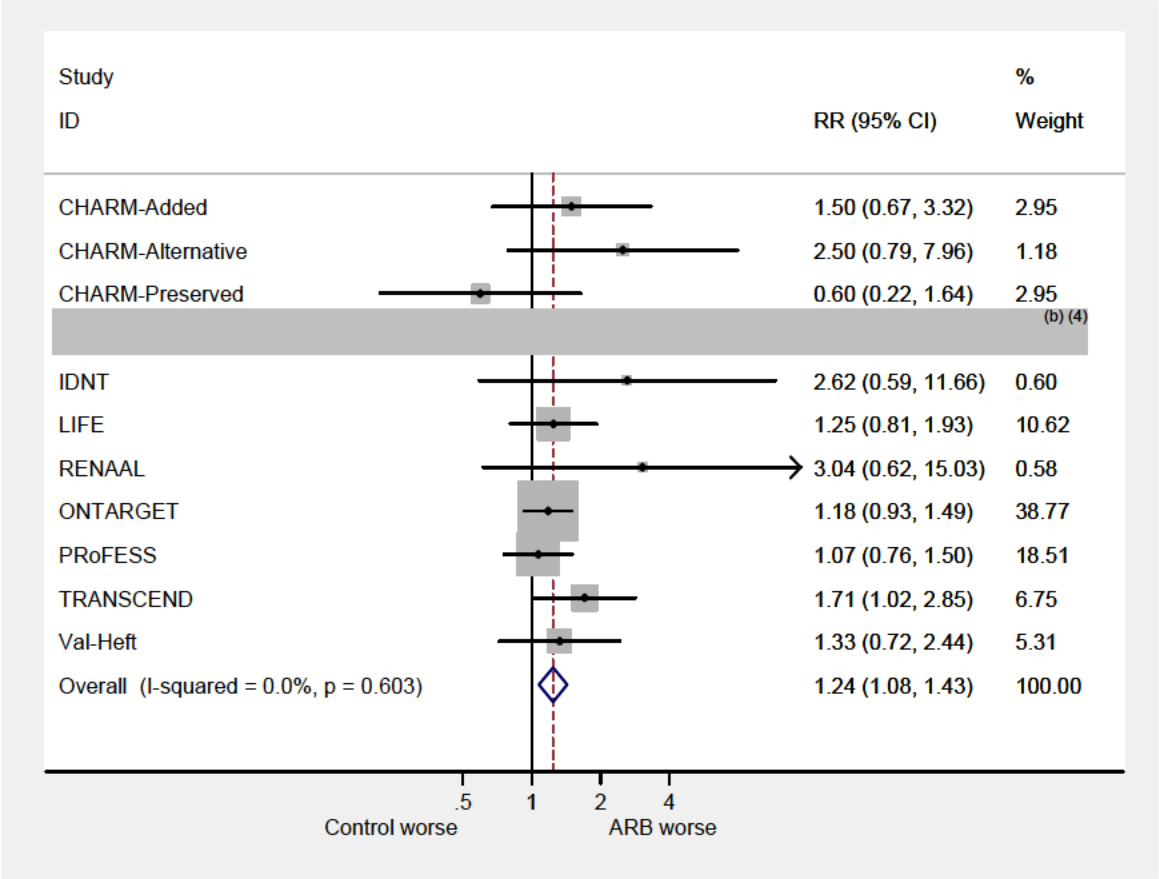
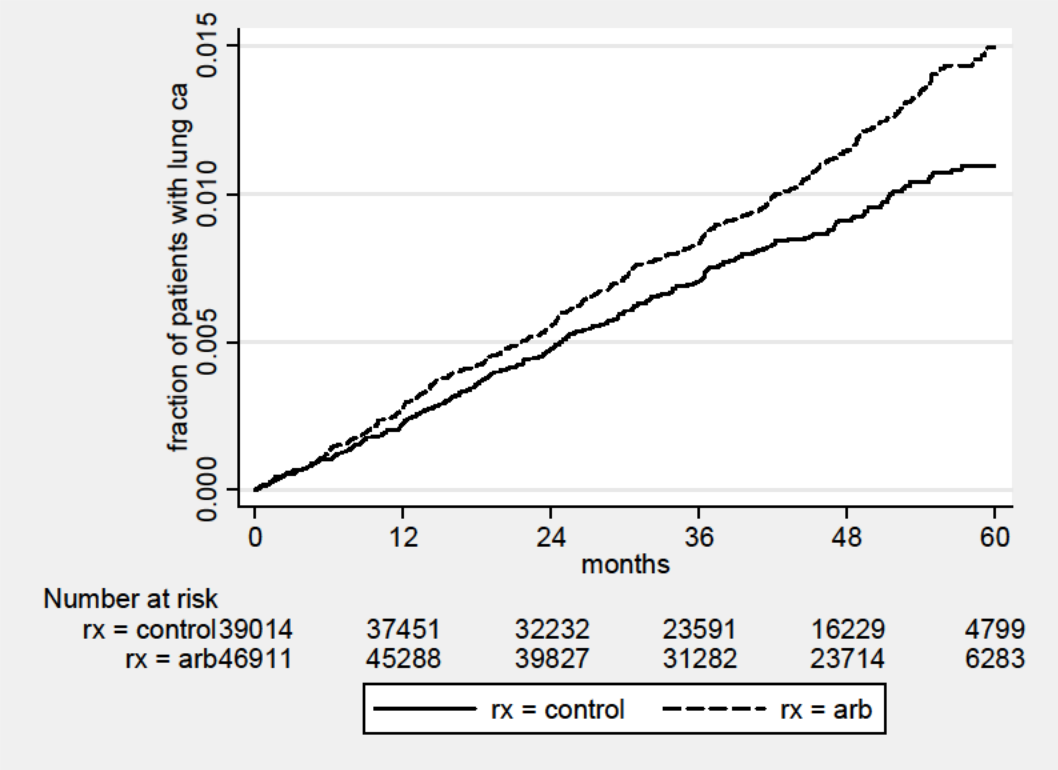


Figure 1: Risk Ratios of Patients with Lung Cancer Events by Trial

I identified new lung cancers during the censoring periods in 645 of the 63,877 patients in the nine trials that captured histories of cancer sites. (PRoFESS did not capture histories of cancer sites. IDNT may have in concomitant diagnoses but the sponsor did not submit to the FDA a dataset with them.) About 97% of the first lung cancer events were new lung cancers in these nine trials. The pooled RR is 1.32 (95% CI 1.12-1.59, p = 0.001). The pooled RR excluding LIFE is 1.33 (95% CI 1.12-1.59, p = 0.001).

I also analyzed new or recurrent lung cancer events separately for the trials excluding most ACEI use (i.e., the trials I use for the prostate cancer and hematologic malignancy meta-analyses) and for the trials including substantial ACEI use. For the five trials excluding most ACEI use the pooled RR is 1.57 (95% CI 1.16-2.13, p = 0.003). For the six trials having substantial ACEI use the pooled RR is 1.16 (95% CI 0.99-1.36, p = 0.074).

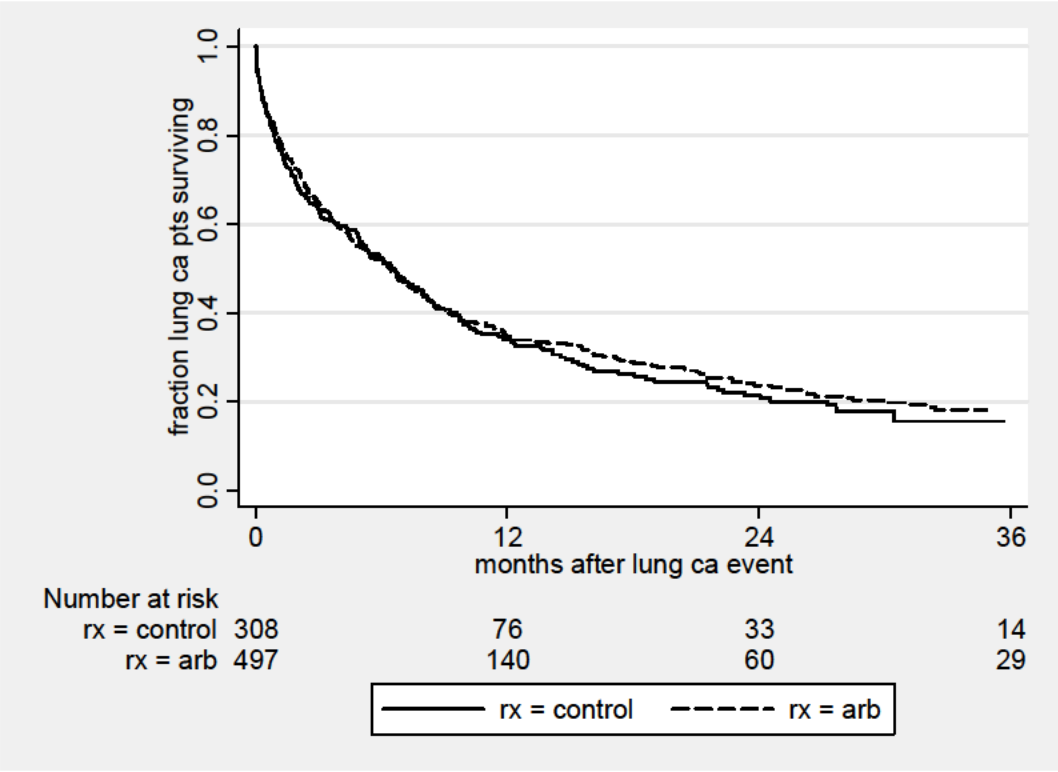
I show the Kaplan-Meier plot of times to first lung cancer events (new or recurrent) in Figure 2. The incidence curves start to diverge at about nine months and then continue to diverge throughout the five years of follow-up in the longest trials. At five years the cumulative hazard estimate is 1.5% for the ARB arms and 1.1% for the control arms, an absolute risk difference of about 0.4%, i.e., about 0.8 excess lung cancer cases per year per 1,000 patients treated.



p = 0.0033 by log rank stratified by study

Figure 2: Times to First Lung Cancer Events

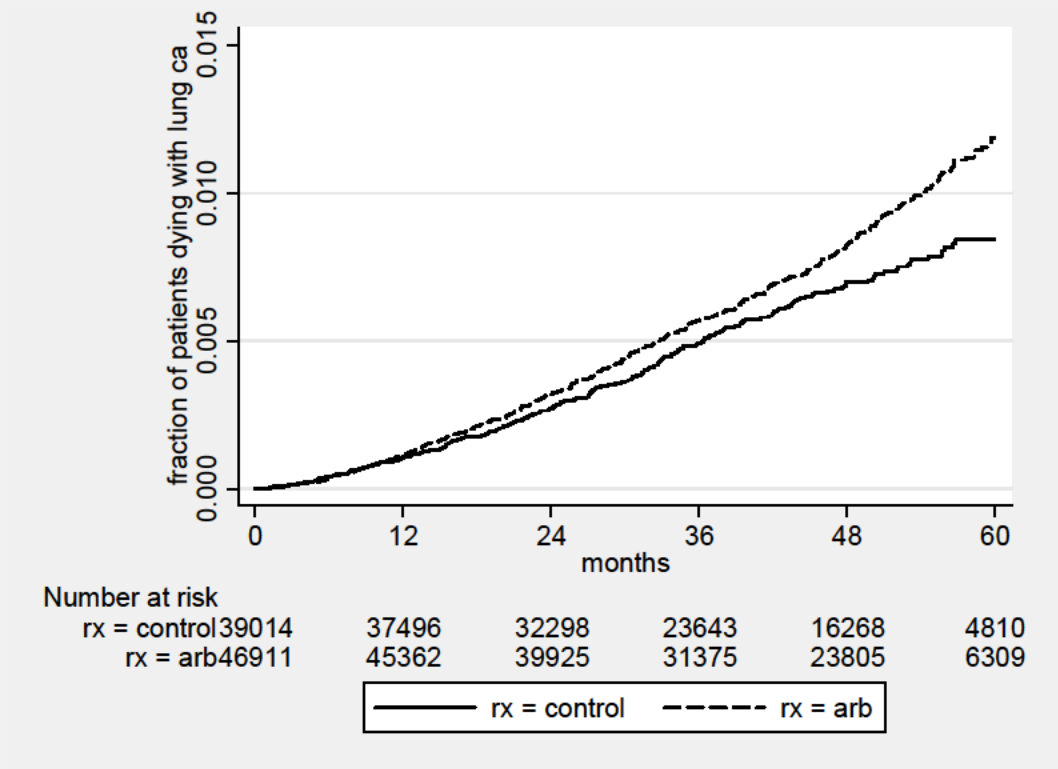
Having a lung cancer event portends a poor prognosis in these studies, similarly poor in the ARB and control arms. I show the Kaplan-Meier plots for survival after a lung cancer event in Figure 3. Survival is dismal, about 34% at one year.



p > 0.7 by log rank stratified by study

Figure 3: Survival after a Lung Cancer Event

Because lung cancer events were more frequent with ARB use while survival after a lung cancer event was similar regardless of ARB use, patients dying with lung cancer were more frequent in the ARB arms. I show the Kaplan-Meier plots for times to patients dying with lung cancer in Figure 4. The hazard ratio (HR) by Cox regression for dying with lung cancer is 1.27 (95% CI 1.08-1.51, p = 0.005).



p = 0.005 by log rank stratified by study

Figure 4: Times to Dying with Lung Cancer

I explored the effects of baseline cofactors upon lung cancer events with Cox regressions stratified by study. The Cox regression including only treatment as a factor produces results similar to the meta-analysis, HR 1.27 (95% CI 1.1-1.46, p = 0.001). For this Cox regression the proportional hazards assumption is not rejected (p > 0.3). I show the results of a Cox regression including treatment and cofactors of age, sex, and smoking status (for the 10 studies having data on smoking, i.e., except Val-Heft) in Table 3.

Table 3: Cox Regression of Times to First Lung Cancer Events

```
No. of subjects =        80915                     Number of obs    =     80915
No. of failures =          763
Time at risk    =    3526808.2                     LR chi2(5)       =    606.00
Log likelihood  =   -8097.0742                     Prob > chi2      =    0.0000

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         ARB |   1.256748   .0938048     3.06   0.002      1.08571    1.454731
         age |    1.06357   .0049333    13.29   0.000     1.053944    1.073283
        male |   1.332871   .1221992     3.13   0.002     1.113651    1.595245
   ex-smoker |   4.404436    .540857    12.07   0.000     3.462297    5.602945
curr. smoker |   10.59602   1.362723    18.35   0.000     8.235168    13.63369
------------------------------------------------------------------------------
                                                        Stratified by study
```

ARB use, age, male sex, and ex- or current smoking status are all associated with higher risks of lung cancer. Whether male sex is an independent risk factor is unclear because men in the trials had much higher rates of smoking than women (71% vs. 32% for any smoking). Cox regressions including interaction terms between ARB use and age, sex, and smoking status produced no statistically significant interactions (all $p > 0.4$). However, the global test for failure of the proportional hazards assumption is significant ($p = 0.003$) with age and ex-smoking status significantly contributing to the failure.

Lung cancer event rates were high for current smokers as shown in Figure 5. At five years the cumulative rate of lung cancer events in baseline current smokers in the ARB arms approaches 4%. The absolute risk difference in smokers at five years was about 1.1% and appears to be accelerating.

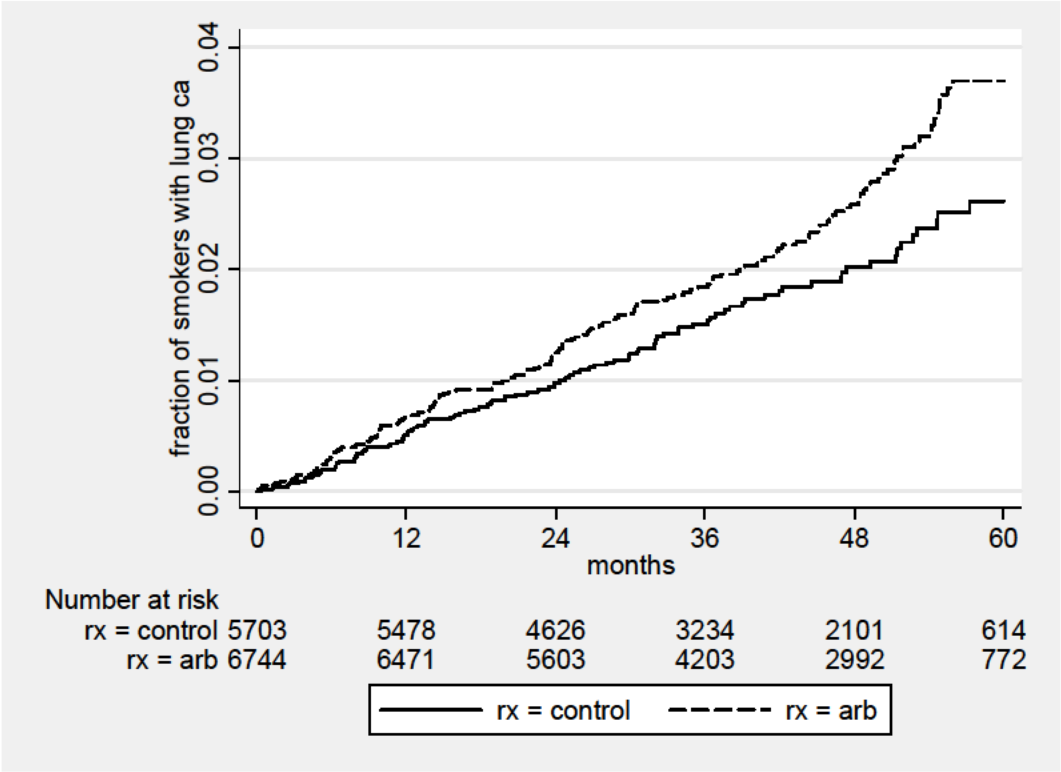


Figure 5: Times to First Lung Cancer Events for Current Smokers at Baseline

To explore age effects I analyzed separately age groups split at the median age of 65. While patients older than 65 at baseline showed proportional hazards for the treatment effect, patients aged 65 or younger showed the pattern depicted in Figure 6. There appears to be an accelerating risk for patients aged 65 or younger. In patients aged 65 or younger most lung cancer events (about 52%) occurred in current smokers while about 20% of these patients were current

smokers. However, late divergences of the curves are seen for both ex-smokers and non-smokers.

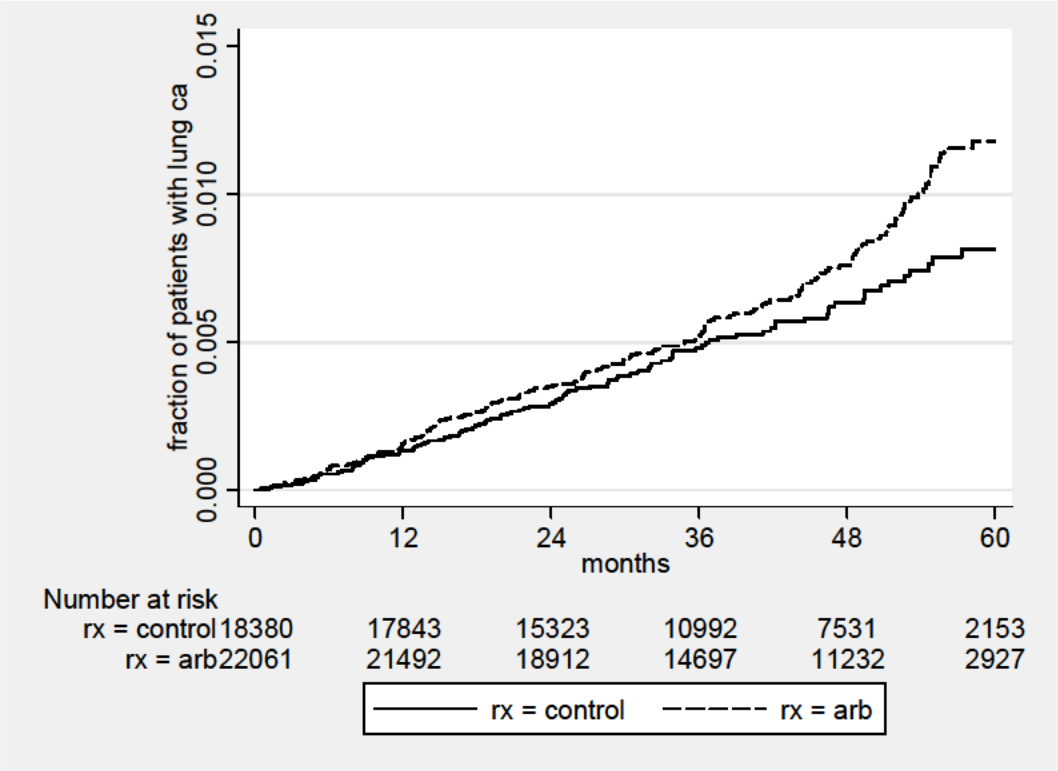


Figure 6: Times to First Lung Cancer Events for Patients 65 or Younger at Baseline

Prostate Cancer

I identified new or recurrent prostate cancer events during the censoring periods in 221 of the 11,087 men in the five trials excluding most ACEI use. The pooled RR comparing the ARB arms to the control arms is 1.23 (95% CI 0.95-1.6, p = 0.13). I show the forest plot of RRs by trial in Figure 7. The pooled RR excluding LIFE (the index study) is 1.36 (95% CI 0.88-2.1, p = 0.15). About 10% of the patients with prostate cancer events had a history of prostate cancer. The pooled RR for new prostate cancers, 1.25, is similar to that for new and recurrent prostate cancers and is also not statistically significant (p = 0.13). The pooled RR for new or recurrent prostate cancers in all 11 trials, including the ones with substantial ACEI use, is 1.04 (p > 0.6).

I show the Kaplan-Meier plot of times to first prostate cancer events (new or recurrent) in Figure 8. There is a suggestion of a slightly higher prostate cancer rate in the ARB arms beginning several months after randomization but some convergence of the curves later.

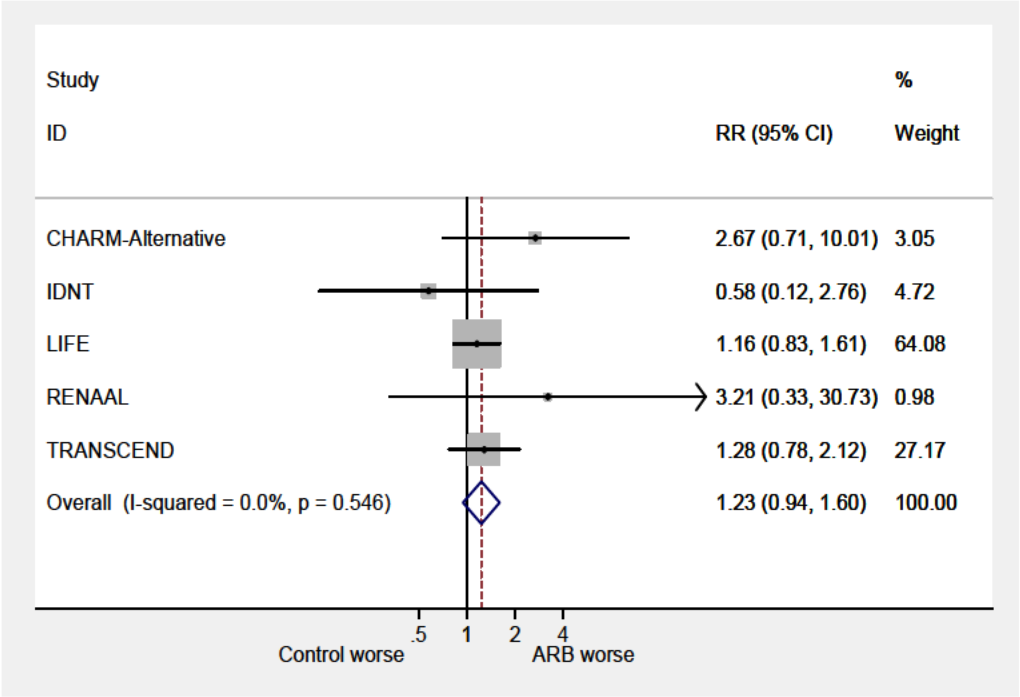
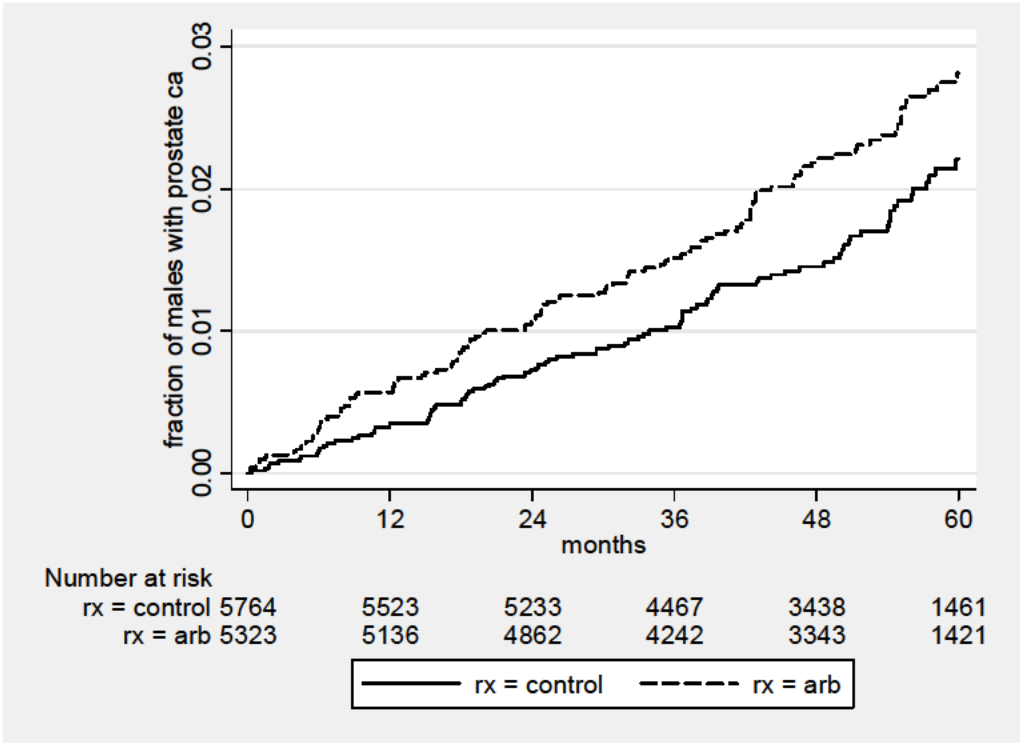


Figure 7: Risk Ratios of Patients with Prostate Cancer Events by Trial



p = 0.12 by log rank stratified by study

Figure 8: Times to First Prostate Cancer Events in Men

Survival after a prostate cancer event, about 81% at two years, was similar in the ARB and control arms. Survival from randomization was not significantly different at two years in men regardless of prostate cancer events or ARB use (about 93%).

Hematologic Malignancies

I identified new or recurrent hematologic malignancy events during the censoring periods in 98 of the 20,376 patients in the five trials excluding most ACEI use. The pooled RR comparing the ARB arms to the control arms is 0.69 (95% CI 0.46-1.03, p = 0.07). I show the forest plot of RRs by trial in Figure 9. The pooled RR excluding LIFE (the index study) is 0.83 (95% CI 0.45-1.53, p >0.5). About 6% of the patients with hematologic malignancy events had a history of hematologic malignancy. The pooled RR for new hematologic malignancies is 0.74 and less significant (p = 0.17). The pooled risk ratio for new or recurrent hematologic malignancies in all 11 trials, including the ones with substantial ACEI use, is 0.97 (p > 0.7).

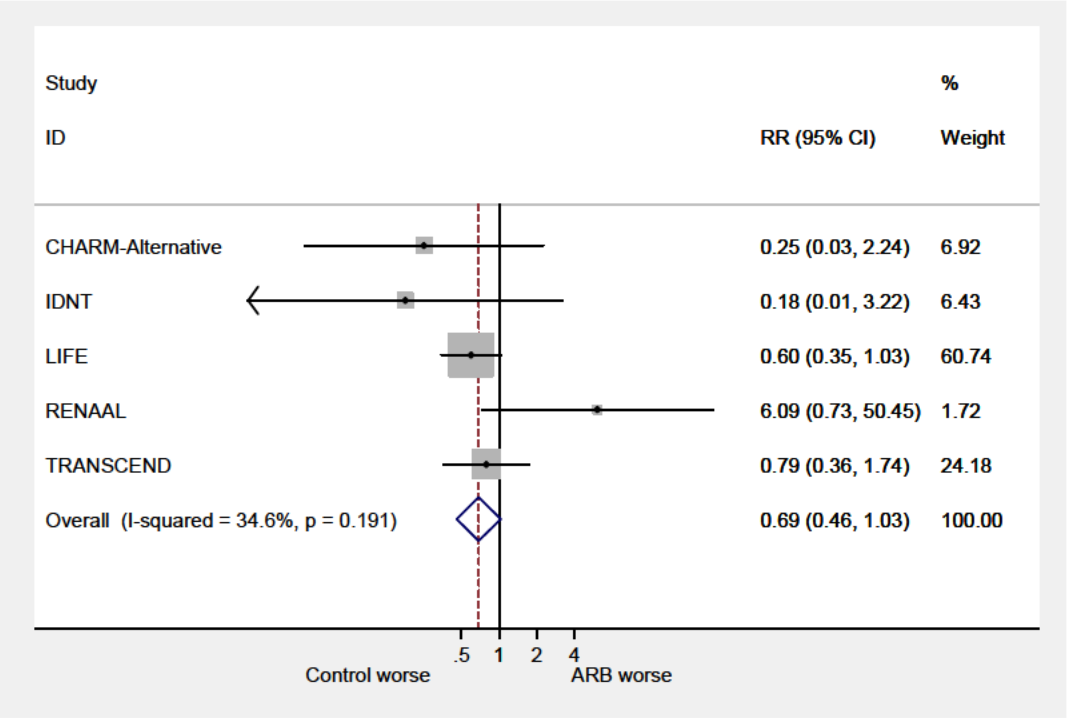
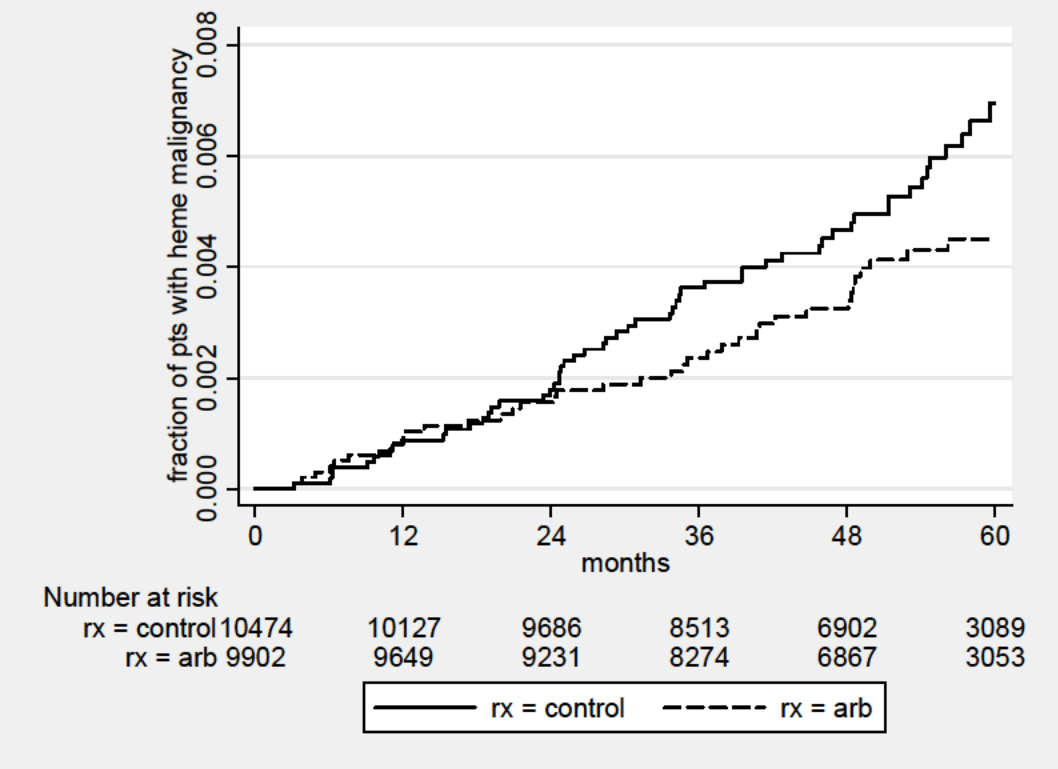


Figure 9: Risk Ratios of Patients with Hematologic Malignancy Events by Trial

I show the Kaplan-Meier plot of times to first hematologic malignancy events (new or recurrent) in Figure 10. The curves diverge after 24 months and remain apart thereafter.



p = 0.06 by log rank stratified by study

Figure 10: Times to First Hematologic Malignancy Events

Survival after a hematologic malignancy event was poor, about 48% at two years, and similar in the ARB and control arms.

Solid Cancers

I identified new or recurrent solid cancer events (excluding non-melanoma skin cancers and brain tumors) during the censoring periods in 4,459 of the 89,925 patients in the eleven trials. The pooled RR comparing the ARB arms to the control arms is 1.05 (95% CI 0.99-1.11, p = 0.10). I show the forest plot of RRs by trial in Figure 11. The pooled RR for all fifteen trials is also about 1.05 (95% CI 0.99-1.11, p = 0.093).

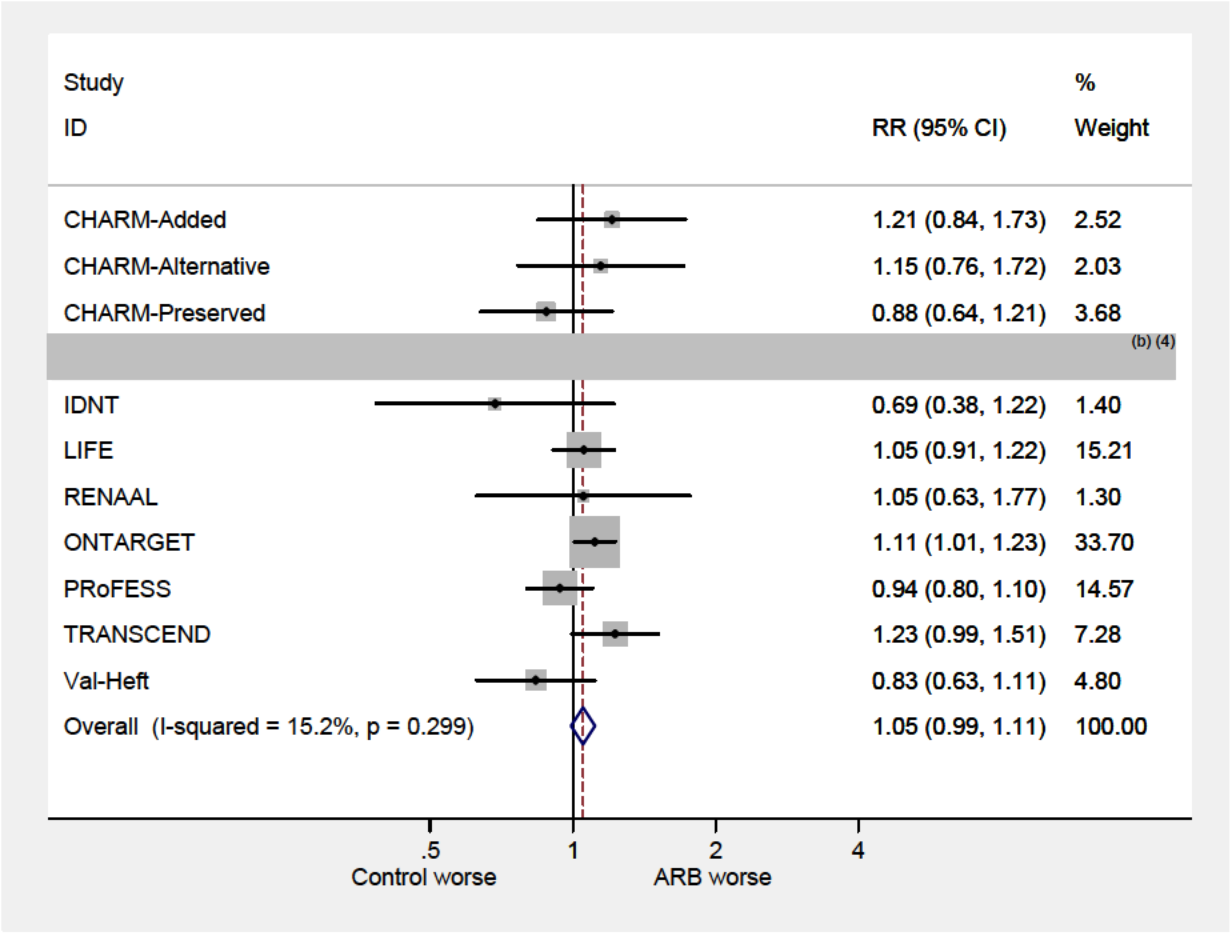
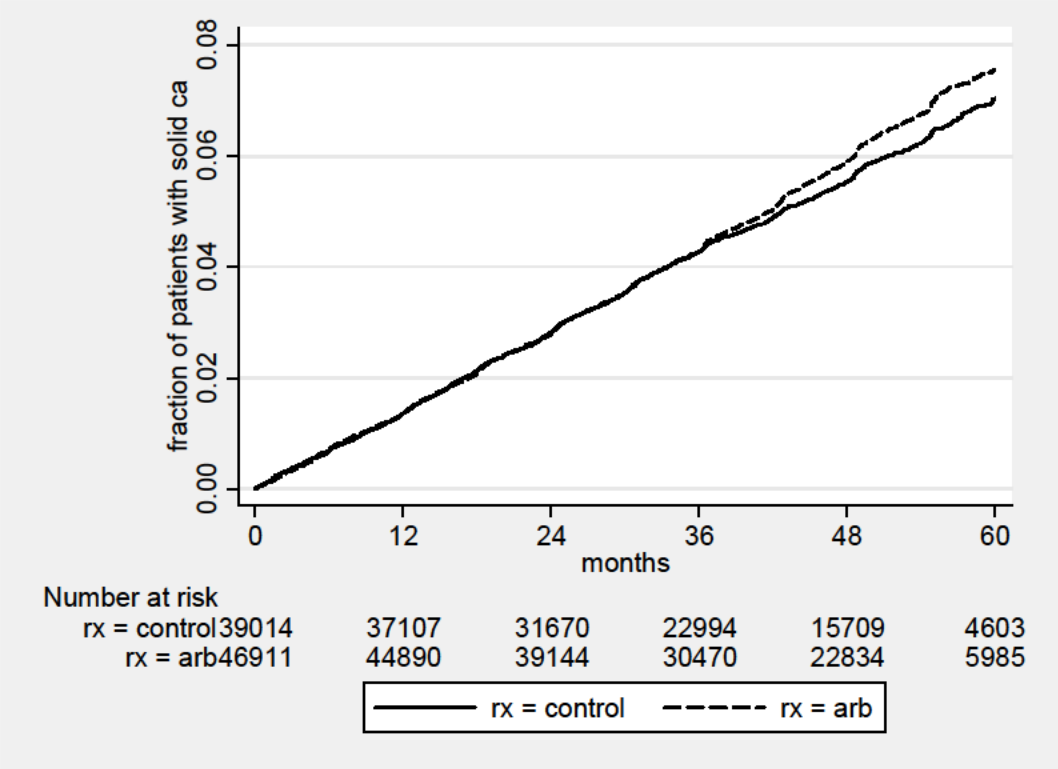


Figure 11: Risk Ratios of Patients with Solid Cancer Events by Trial

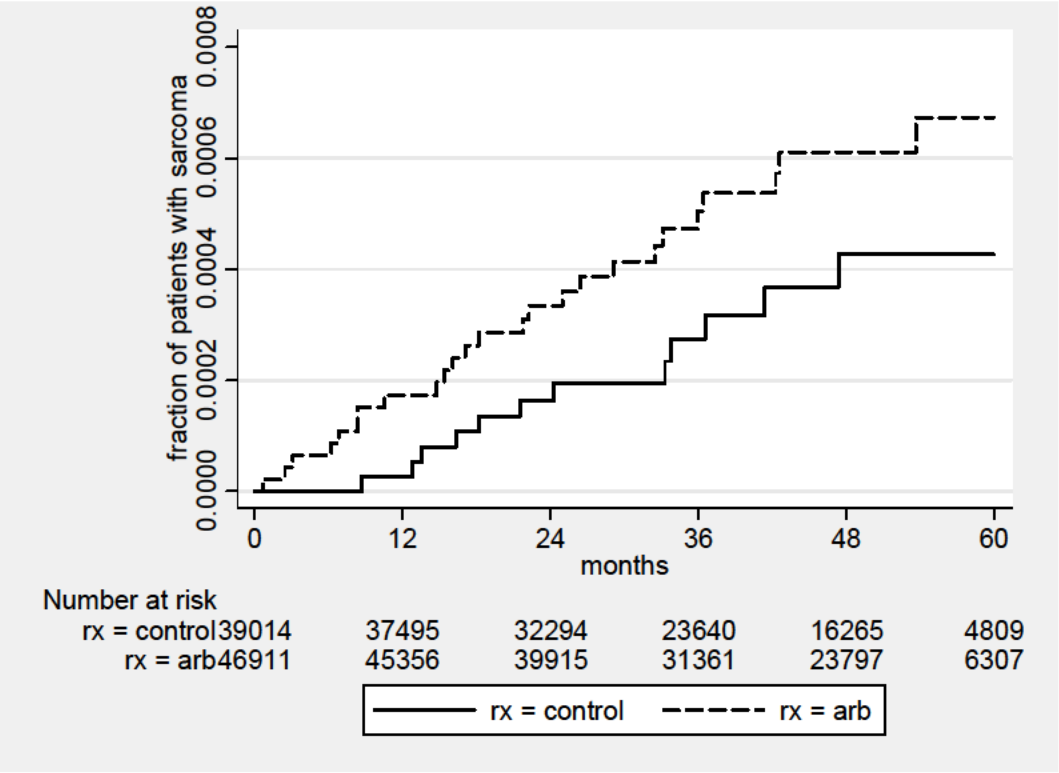
I show the Kaplan-Meier plot of times to first solid cancer events (new or recurrent) in Figure 12. There appears to be slight late divergence of the curves, but the divergence is not statistically significant. The survival curves after a solid cancer event are virtually identical regardless of ARB use (HR 0.99, $p > 0.8$).



p = 0.12 by log rank stratified by study

Figure 12: Times to First Solid Cancer Events

I examined cross-tabulations of the sites of the first solid cancer events by ARB use as exploratory analyses of whether any other specific solid cancer events are imbalanced by ARB use. In addition to lung and prostate cancers sarcomas were imbalanced, with a pooled RR of about 1.8 and p value of 0.081 for eight of the 11 trials having sarcomas and 0.043 for 10 trials having sarcomas. I show the Kaplan-Meier plot of times to first sarcoma events in Figure 12. The incidence curves diverge immediately.



p = 0.037 by log rank stratified by study

Figure 13: Times to First Sarcoma Events

Discussion

ARB use appears to be associated with an increased incidence of lung cancer. The p value for the primary meta-analysis of RR is low ($p = 0.003$) and consistent with a time-to-first-event analysis by a log rank test stratified by study ($p = 0.0033$). The identical meta-analysis except excluding the index LIFE study produces the same estimate for the RR and a similar, highly statistically significant p value ($p = 0.005$). The increased risk of lung cancer with ARBs is robust to sensitivity analyses including a meta-analysis of all 15 large ARB outcome trials that collected cancer sites. The shapes of the incidence curves are consistent with a cancer promoter effect, i.e., delayed initial divergence of the rates in ARB and control arms followed by continuing divergence throughout the duration of follow-up.

The estimate of overall effect size is modest, about a 24% increase in lung cancer incidence. However, some analyses suggest an increasing effect size with increasing duration of therapy. Because ARBs are indicated for life-long treatment (e.g., hypertension, diabetic nephropathy) any consistent or increasing effect upon cancer rates is concerning. The absolute risk difference during the first five years of treatment in the trial populations as a whole is small, i.e., about 0.8 excess lung cancer cases per year per 1,000 patients treated. However, in subgroups at risk for lung cancer, i.e., smokers, the absolute risk increase exceeds 1% at five years. Furthermore, survival following a lung cancer event is dismal, about 34% at one year, and significantly more ARB patients died with lung cancer.

While these absolute risks may not outweigh the cardiovascular benefits of blood pressure reduction in hypertensive patients, there are many other alternative antihypertensives. I believe that these effects of ARBs upon lung cancer should not be ignored and that patients and providers should be fully informed about the risk.

The results regarding prostate cancer are inconclusive. None of the analyses are statistically significant or close to statistically significant. However, because the number of prostate cancer events in the trials excluding most ACEI use and submitted to the FDA is not large and hence the power of these analyses is low and because the results in the non-index trials are supportive, we can not reject definitively an effect of ARBs upon prostate cancer. Additional investigation of this hypothesis is justified. For prostate cancers there is some reassurance: The analyses suggest that, regardless of whether there is some effect of ARBs upon prostate cancer incidence, the effect is not greatly concerning because the data do not suggest a statistically or clinically significant effect upon mortality. Lung cancer, not prostate cancer, appears to be the significant concern for ARBs.

The results regarding hematologic malignancies are also inconclusive. The pre-specified meta-analysis is not statistically significant ($p = 0.07$) but the Kaplan-Meier plot in Figure 10 of times to first hematologic malignancy events is somewhat consistent with a tumor suppressor effect.

For both prostate cancers and hematologic malignancies the inconsistent trial is one of the diabetic nephropathy trials, IDNT or RENAAL. The hematologic malignancy hypothesis, like the one for prostate cancer, needs additional investigation.

The results regarding all solid cancers (excluding non-melanoma skin and brain tumors) are inconclusive but not inconsistent with the lung cancer results. There is a trend towards more solid cancers with ARB use but this may reflect the increased incidence of lung cancers (and possibly prostate cancers.) The sarcoma differences may be chance variations because the incidence curves diverge immediately before we would expect to detect a cancer promotion effect. However, following-up on this possible association is also appropriate.

I did not hypothesize regarding possible effects of dosage because most trials tested the maximum approved dosages and the dosage ranges tested in a few trials were limited to two-fold. In fact, all eleven of the trials included in the primary meta-analyses tested the maximum approved dosages. Of the other trials IRMA 2 tested both maximum and half maximum dosages (b) (4) IRMA 2 is too small, and confounded by poor follow-up, to provide any insight into effects of dosage. (b) (4)

For the prostate cancer and hematologic malignancy hypotheses I postulated that the effects, if real, would be shared with ACEIs. The data appear to support this belief because the analyses including the trials with substantial ACEI use produce RRs very close to 1.0 for both prostate and hematologic malignancies. The picture is less clear for lung cancers. The RR is higher and more significant in the five trials excluding most ACEI use than in the six trials having substantial ACEI use. Whether this is a real difference or a chance effect or related to the differing trial designs and conduct is unclear. For lung cancer we might also speculate that there could be a detection bias with ACEIs resulting from ACEI-induced cough. Other studies have usually not associated ACEI use with a higher risk of cancer. (Grossman, Messerli et al. 2002; Sipahi, Chou et al. 2011) However, we can make a similar statement for ARB use and cancer.

The strengths of this study are that I pre-specified well-defined hypotheses to test and an analytical plan providing details on cancer ascertainment and censoring, I had access to and utilized fully the raw trial data to resolve ambiguities in cancer ascertainment, and I performed patient-level meta-analyses and time-to-event and survival analyses with baseline cofactor explorations. The use of raw trial data is also a limitation because I analyzed only trials submitted to the FDA with such data. While there could be a "submission bias" analogous to a "publication bias", my expectation is that a submission bias would decrease the likelihood of finding an association between ARB use and cancer: If a drug company observed that a clinical trial of an ARB had a suspicious association between an ARB and cancer, the company should

be less likely rather than more likely to submit such a study for FDA review. In fact I believe that the drug companies did not consider cancer events in determining whether or not to submit a trial to the FDA but based their decisions to submit on the targeted efficacy indications and their business goals.

One internal FDA criticism of all of the ARB and cancer meta-analyses is that they are "fishing expeditions" (see email reproduced in Appendix 2) with severe multiplicity issues. However, as I described in the Introduction, I had identified lung cancer as a potential problem for losartan based on my review in 2002 of the LIFE trial. I formulated the lung cancer hypothesis based on the LIFE trial results; I provide documentation of the lung cancer hypothesis in Appendix 2. The one valid criticism is that the most appropriate meta-analysis may be the one excluding the LIFE trial. Because the results for that analysis are highly supportive of a lung cancer risk with ARB use, I argue that multiplicity is not an issue for the principal finding of an increased risk of lung cancer with ARB use.

Another potentially controversial aspect of the analytical plan is the decision to exclude trials because of data quality issues. I believe that the justifications of the exclusion of the five trials are valid and I provide documentation of them as Appendix 1 to this review. However, regardless of whether one considers the exclusions to be appropriate or not, they do not affect the conclusion that some ARBs appear to be associated with a higher incidence of lung cancer; they only affect the conclusion that ARBs as a class have this association. Adding to the meta-analyses the one small irbesartan trial excluded (IRMA 2) changes the results minimally. Hence for the four ARBs contributing the bulk of the data to the primary meta-analyses (candesartan, irbesartan, losartan, and telmisartan) we should have confidence that their use is associated with an increased incidence of lung cancer. Furthermore, the meta-analysis of all 15 trials that collected cancer sites for malignancies (i.e., all trials with data submitted to the FDA except VALIANT) produces a pooled RR of 1.16 and a p value of 0.027. The cancer site data submitted to the FDA are consistent with a class effect on lung cancers.

That missing trials should not negate the association between ARB use and lung cancer is illustrated strikingly by the missing losartan trials. In response to an FDA request Merck initially submitted trial-level data from five losartan clinical outcome studies conducted by Merck: LIFE and RENAAL (with raw data from prior submissions and included in these meta-analyses) (b) (4) I commented in the Introduction that the ARB Trialists Collaboration analyzed only LIFE and, while Bangalore *et al.* analyzed LIFE and RENAAL, they mis-referenced and mis-counted incident cancer cases in RENAAL: Bangalore *et al.* counted only seven cancer cases (actually drug withdrawals for cancer) while I verified from the raw data 55 solid cancers excluding brain and non-melanoma skin cancers. The lung cancer RRs for all five of the trials in the Merck initial submission exceed 1, (b) (4) to 3.0 for RENAAL (b) (4)

(b) (4) The pattern of lung cancer trial RRs, i.e., 10 of 11 trials with RRs exceeding 1 in the primary meta-analysis and two more larger losartan trials with RRs exceeding 1 in the Merck submission (for four out of four larger losartan trials with RRs exceeding 1), supports that ARB use, in particular losartan, is associated with an increased risk of lung cancer.

While we lack good data definitively confirming or refuting an association with lung cancer for four FDA-approved ARBs (azilsartan, eprosartan, olmesartan, and valsartan), the one study with valid data for valsartan (Val-Heft) has a RR estimate for lung cancer nearly identical to the primary meta-analysis. (b) (4) The association of ARBs with lung cancer remains significant in a meta-analysis of all 15 trials collecting cancer sites and having complete data submitted to the FDA. I conclude that the increased incidence of lung cancers with ARB use is likely a class effect of ARBs and that it would be inappropriate to classify azilsartan, eprosartan, olmesartan, and valsartan as safe because of their lack of adequate studies.

References

(b) (4)

ARB_Trialists_Collaboration (2011). "Effects of telmisartan, irbesartan, valsartan, candesartan, and losartan on cancers in 15 trials enrolling 138,769 individuals." J Hypertens 29(4): 623-35.

Bangalore, S., S. Kumar, et al. (2011). "Antihypertensive drugs and risk of cancer: network meta-analyses and trial sequential analyses of 324,168 participants from randomised trials." Lancet Oncol 12(1): 65-82.

Bomback, A. S. and P. J. Klemmer (2007). "The incidence and implications of aldosterone breakthrough." Nat Clin Pract Nephrol 3(9): 486-92.

Brenner, B. M., M. E. Cooper, et al. (2001). "Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy." N Engl J Med 345(12): 861-9.

Cohn, J. N. and G. Tognoni (2001). "A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure." N Engl J Med 345(23): 1667-75.

Coleman, C. I., W. L. Baker, et al. (2008). "Antihypertensive medication and their impact on cancer incidence: a mixed treatment comparison meta-analysis of randomized controlled trials." J Hypertens 26(4): 622-9.

Dahlof, B., R. B. Devereux, et al. (2002). "Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol." Lancet 359(9311): 995-1003.

Dickstein, K. and J. Kjekshus (2002). "Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan." Lancet 360(9335): 752-60.

FDA. (2007). "FDA Backgrounder for the December 11-12, 2007 meeting of the Cardio-Renal Drugs Advisory Committee" Retrieved March 4, 2013, from http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4327b1-02-fda-backgrounder.pdf.

FDA. (2011, June 2, 2011). "FDA Drug Safety Communication: No increase in risk of cancer with certain blood pressure drugs--Angiotensin Receptor Blockers (ARBs)." Retrieved June 6, 2011, from http://www.fda.gov/Drugs/DrugSafety/ucm257516.htm.

Granger, C. B., J. J. McMurray, et al. (2003). "Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial." Lancet 362(9386): 772-6.

Grossman, E., F. H. Messerli, et al. (2002). "Carcinogenicity of antihypertensive therapy." Curr Hypertens Rep 4(3): 195-201.

Haller, H., S. Ito, et al. (2011). "Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes." N Engl J Med 364(10): 907-17.

Harris, R. J., M. J. Bradburn, et al. (2008). "metan: fixed- and random-effects meta-analysis." Stata Journal 8(1): 3-28.

Husten, L. (2012, September 26, 2012). "Merck Returns To Cardiome All Rights To Atrial Fibrillation Drug Vernakalant." Retrieved March 4, 2013, from http://www.forbes.com/sites/larryhusten/2012/09/26/merck-returns-to-cardiome-all-rights-to-atrial-fibrillation-drug-vernakalant/.

Imai, E., J. C. Chan, et al. (2011). "Effects of olmesartan on renal and cardiovascular outcomes in type 2 diabetes with overt nephropathy: a multicentre, randomised, placebo-controlled study." Diabetologia 54(12): 2978-86.

Leshem-Rubinow, E., A. Steinvil, et al. (2012). "Association of Angiotensin-Converting Enzyme Inhibitor Therapy Initiation With a Reduction in Hemoglobin Levels in Patients Without Renal Failure." Mayo Clin Proc.

Lewis, E. J., L. G. Hunsicker, et al. (2001). "Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes." N Engl J Med 345(12): 851-60.

Marciniak, T. A. (2003, January 15, 2003). "Amended Clinical Review, Supplemental NDA Submission, NDA 20-386." Retrieved November 23, 2012, from http://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/20-386S032_Cozaar_medr_P1.pdf.

McMurray, J. J., R. R. Holman, et al. (2010). "Effect of valsartan on the incidence of diabetes and cardiovascular events." N Engl J Med 362(16): 1477-90.

McMurray, J. J., J. Ostergren, et al. (2003). "Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial." Lancet 362(9386): 767-71.

Nissen, S. E. (2010). "Angiotensin-receptor blockers and cancer: urgent regulatory review needed." The Lancet Oncology 11(7): 605-606.

Parving, H.-H., H. Lehnert, et al. (2001). "The Effect of Irbesartan on the Development of Diabetic Nephropathy in Patients with Type 2 Diabetes." New England Journal of Medicine 345(12): 870-878.

Pfeffer, M. A., J. J. McMurray, et al. (2003). "Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both." N Engl J Med 349(20): 1893-906.

Remuzzi, G., P. Ruggenenti, et al. (2004). "Continuum of renoprotection with losartan at all stages of type 2 diabetic nephropathy: a post hoc analysis of the RENAAL trial results." J Am Soc Nephrol 15(12): 3117-25.

Sipahi, I., J. Chou, et al. (2011). "Meta-analysis of randomized controlled trials on effect of angiotensin-converting enzyme inhibitors on cancer risk." Am J Cardiol 108(2): 294-301.

Sipahi, I., S. M. Debanne, et al. (2010). "Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials." Lancet Oncol 11(7): 627-36.

Wood, S. (2010, October 25, 2010). "ACT 5 vernakalant trial suspended." Retrieved March 4, 2013, from http://www.theheart.org/article/1140055.do.

Wood, S. (2011, June 2, 2011). "FDA review concludes: No cancer risk with ARBs." Retrieved November 19, 2012, 2012, from www.theheart.org/article/1234673/print.do.

Yusuf, S., H. C. Diener, et al. (2008). "Telmisartan to prevent recurrent stroke and cardiovascular events." N Engl J Med 359(12): 1225-37.

Yusuf, S., M. A. Pfeffer, et al. (2003). "Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial." Lancet 362(9386): 777-81.

Yusuf, S., K. K. Teo, et al. (2008). "Telmisartan, ramipril, or both in patients at high risk for vascular events." N Engl J Med 358(15): 1547-59.

Appendix 1: Justifications for the Exclusions of Five Studies from the Angiotensin Receptor Blockers and Cancer Meta-analysis

IRMA-2 (The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes.)

The NEJM publication reports the completeness of follow-up ambiguously: "A total of 30 patients in the placebo group, 27 in the group assigned to receive 150 mg of irbesartan per day, and 20 in the group assigned to receive 300 mg of irbesartan per day withdrew from the study for various reasons (Fig. 1)." In Figure 1 an additional 18 patients had no measurement of albuminuria and 3 received no drug treatment. The numbers "Completed study" are 171, 168, and 174 in Figure 1. By these numbers (171+168+174)/611 = 84% completed the study. However, four of the incomplete follow-ups were deaths, so 85% represents better the percentage with complete follow-up.

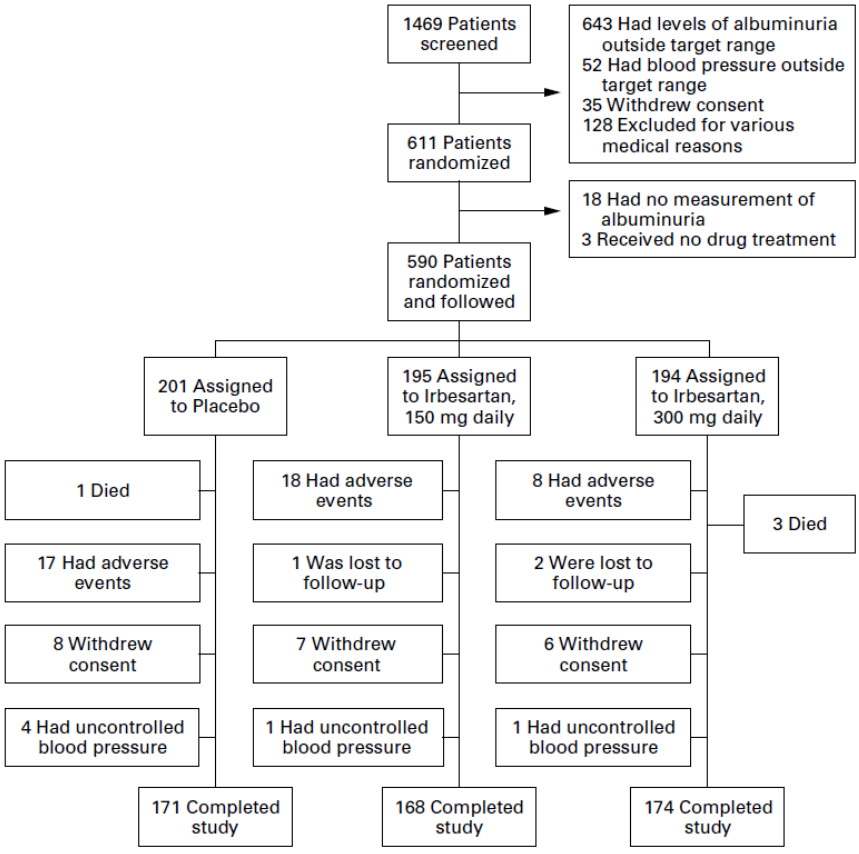


Figure 1. Profile of the Trial.
All 590 patients who underwent randomization and follow-up were included in the intention-to-treat analyses.

The ambiguity is that neither the study report nor the publication defines explicitly what "withdrew from the study" or not "completed study" represents. It is obvious that these patients didn't complete treatment, but did they have follow-up adequate for determining cancer events? The study report states the following:

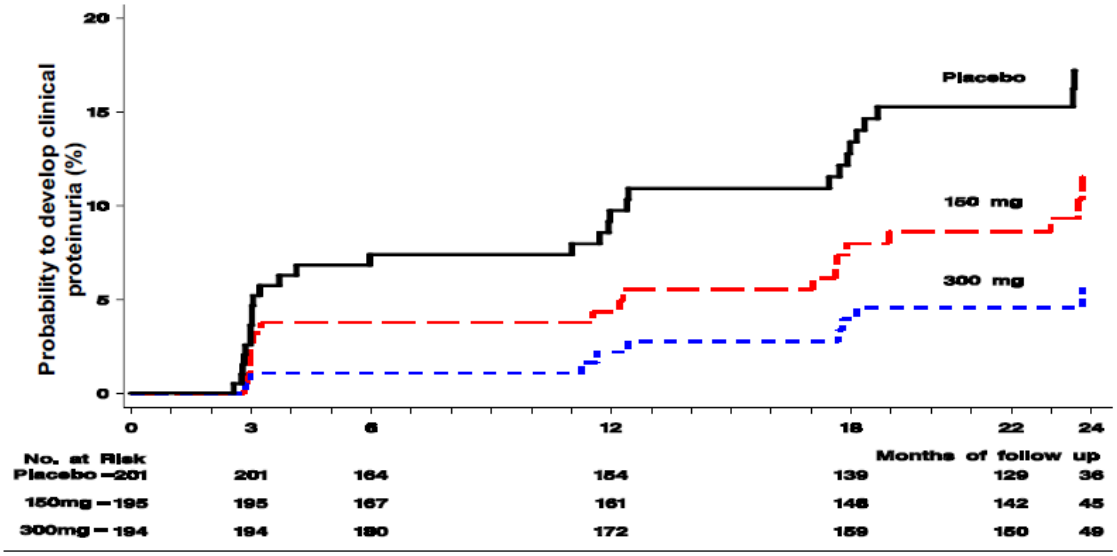
> "In the main study and GFR sub-study, AEs occurring within 10 days after study drug discontinuation were reported to the Sponsor. In the GFR extension study, AEs occurring within 4 weeks of study drug discontinuation were reported to the Sponsor."

It also states:

> "Additionally, all subjects prematurely withdrawn from the study were assessed for survival and nephrology status 2 years after the date of randomization with the exception of those who were lost-to-follow-up or deceased (added by Amendment No. 9)."

The study report has the following figure:

Figure 10.1.1.2 Estimates of Probability to Develop Clinical Proteinuria: Intent-to-Treat Subjects

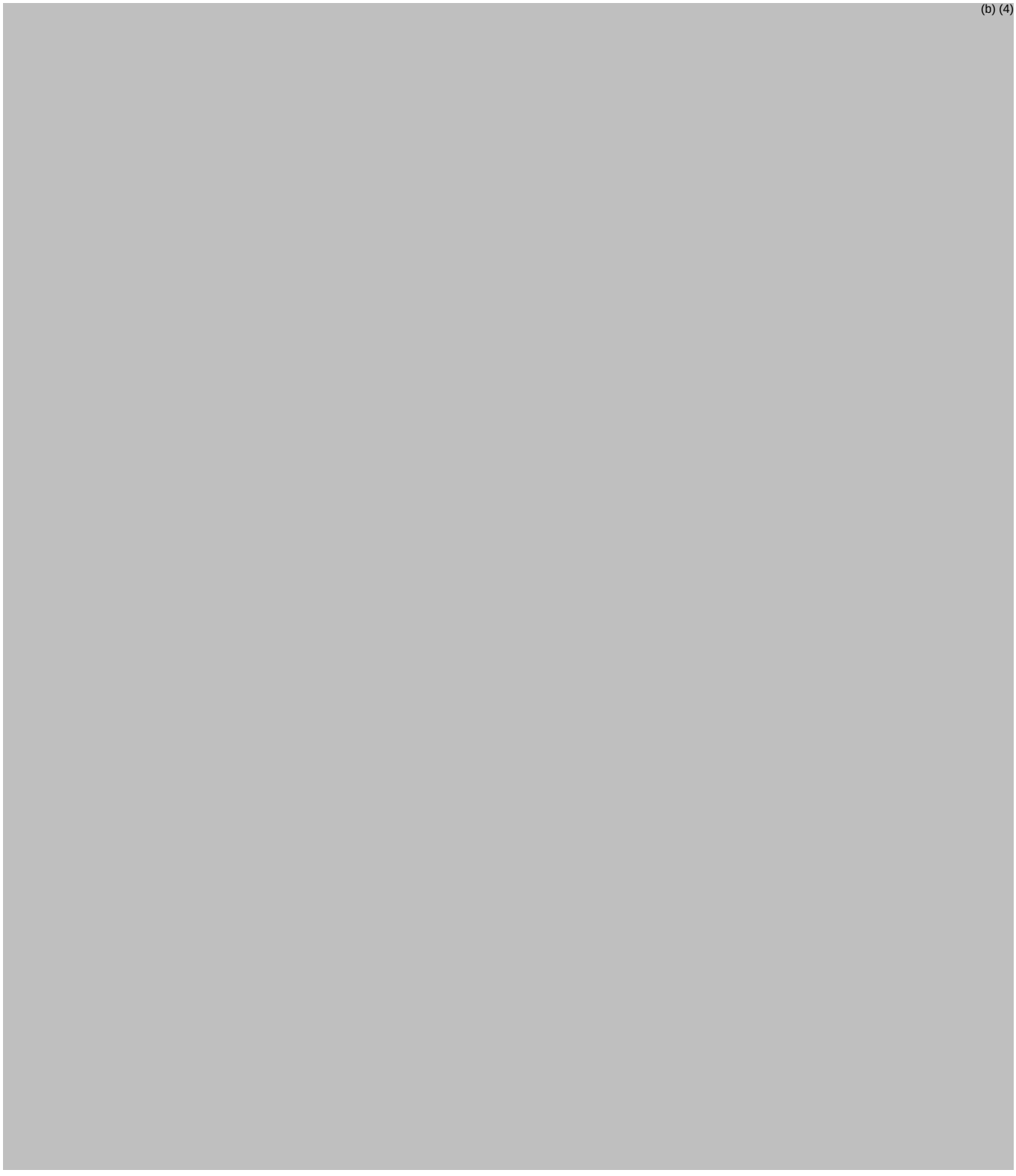


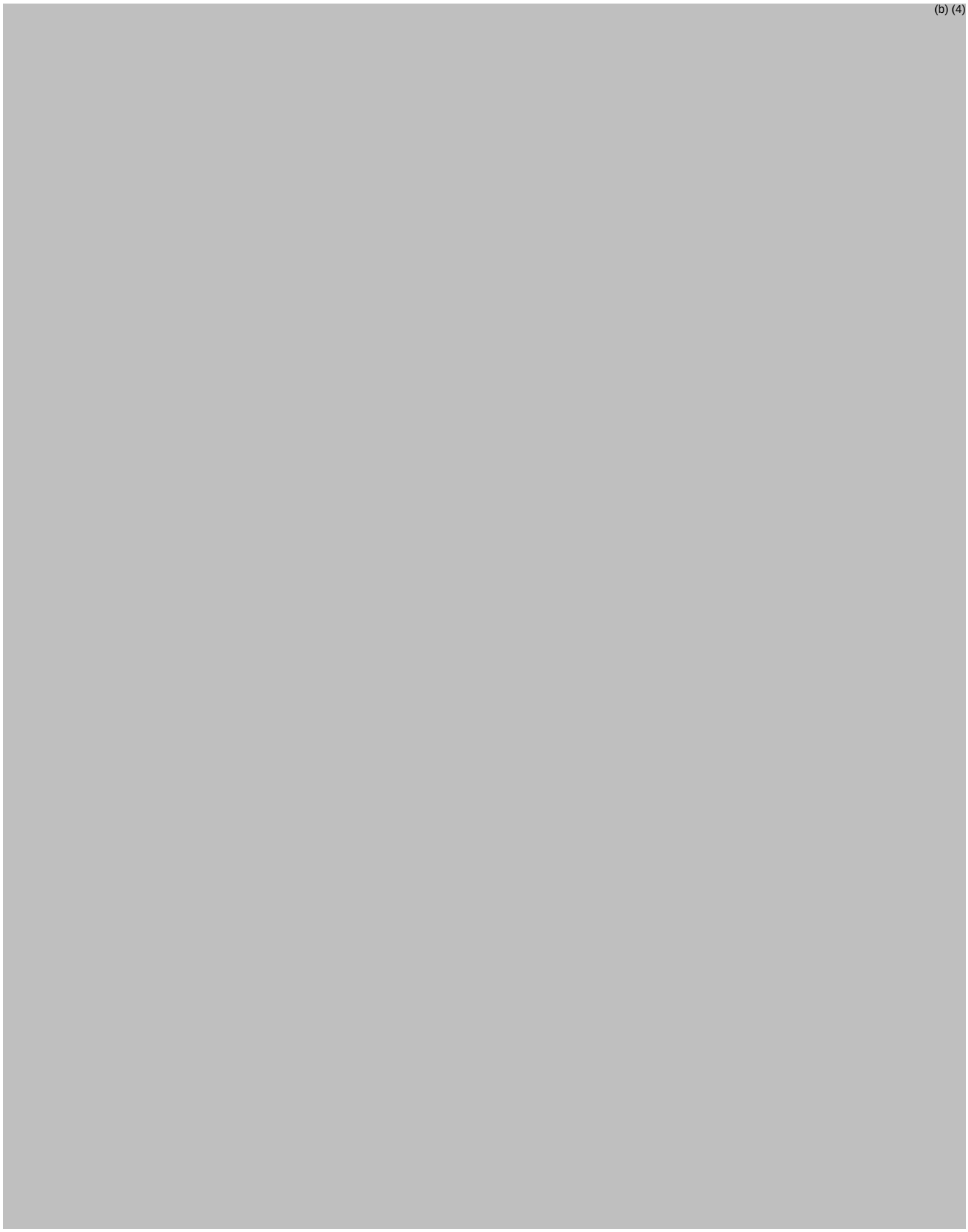
EFC2481
Dataset: Intent-to-Treat Subjects
Source: Appendix 10.1.11.3
Note: The sample size at Month 24 declines because most subjects completed Visit 9 at Month 22. Thus, this decline in sample does not indicate premature discontinuation of these subjects from the study.

Note the low numbers at risk at month 24 (IRMA 2 was reported as a 2-year study) and the explanation in the footnote in the figure.

I interpret the above as that IRMA 2 did not collect AE information 10 days to 4 weeks after treatment discontinuation. Follow-up was early even in those counted as completing the two year study. The 85% complete (about 15% incomplete) likely represents an optimistic estimate of the completeness of follow-up. IRMA 2 fails the pre-specified criterion that incompleteness of follow-up not exceeds 10%.

(b) (4)




(b) (4)

VALIANT (Multinational, multicenter, double-blind, randomized, active controlled, parallel group study comparing the efficacy and safety of long-term treatment with valsartan, captopril and their combination in high-risk patients after myocardial infarction.)

VALIANT has incomplete cancer ascertainment. The reasons for the incomplete cancer ascertainment are complicated and dependent upon the trial design, particularly how adverse event data were collected—or not collected. The most relevant section from the sponsor's "Response to FDA information request: cancer data for valsartan" dated 06-Oct-2010 is the following:

4 Ascertainment scheme for cancer

FDA request

"Comment on the ascertainment scheme for cancer."

Novartis response

Val-HeFT, VALIANT (b) (4)

For the above-mentioned studies, all coding of investigator reported terms was re-mapped to the Medical Dictionary for Regulatory Activities (MedDRA) version 13.0, which is the latest version of MedDRA available at Novartis. Adverse events consistent with solid organ tumors were identified by the use of the Maintenance and Support Services Organization (MSSO) Standardized MedDRA Query (SMQ) "Malignant or unspecified tumors" (Narrow Search MedDRA version 13.0). Per FDA's request, all MedDRA Preferred Terms, considered to be related to hematologic/ liquid tumors, were deleted from the SMQ. Preferred terms consistent with hematologic tumors (e.g. leukemia, lymphomas and myelomas) were identified as hematological malignancies using the most recent International Classification of Diseases for Oncology and are presented in Appendix 1. As a result, 365 of the 1814 preferred terms for malignant or unspecified tumors, in the Narrow Standardized MedDRA version 13, were excluded.

Information on the most frequent MedDRA preferred terms is included for each study to provide additional data on cancer type. In addition, we have included information, using the Narrow Search MedDRA version 13 SMQ, on the incidence of breast neoplasms, malignant and unspecified SMQ, prostate neoplasms, malignant and unspecified SMQ, and lung cancer for these specific cancer types. This information was previously provided in the June 24, 2010 letter sent to FDA. As there is no specific SMQ for lung cancer in MedDRA 13, preferred terms selected by Novartis medical reviewers are used (Appendix 2).

Protocols [redacted] (b) (4) were not mapped to the narrow MedDRA terms as noted above. The cancer adverse events were taken directly from the post-text adverse event tables, as an electronic MedDRA coded dataset was unavailable.

The sponsor's response completely neglects how the cancer events were captured in the valsartan trials. For VALIANT event capture was complicated and ambiguously specified. The protocol specified the following regarding collection of adverse events:

Adverse events

Adverse events will be recorded in the CRF or the Serious Adverse Event (SAE) form if they meet the following criteria:

- Primary and secondary efficacy parameters (as described in Section 3.5.2)
- Pre-specified safety and tolerability parameters (known side effects of either captopril and/or valsartan) as described in the previous section
- Serious adverse events (as described in the following section).

Other non-serious adverse events will not be collected in the CRF. However, information

The criteria for SAEs were the usual regulatory ones with the criteria most applicable to malignancies being fatal or requiring or prolonging hospitalization. However, note that the first method for recording AEs above is "Primary and secondary efficacy parameters". The relevant ones from Section 3.5.2 are the following:

Primary efficacy parameters

The primary efficacy parameter is all-cause mortality (time to death).

Secondary efficacy parameters

Secondary efficacy parameters are as follows:

- All-cause (unplanned and elective) hospitalization

Death and all-cause hospitalizations were the first primary and first secondary efficacy parameters. However, where investigators should have recorded malignancies (on the efficacy and death CRFs or some other CRF) is ambiguous per the following directions reiterated for each visit:

- For adverse events occurring since the last visit:
  - ◊ Complete the Serious Adverse Event CRF for any serious adverse events that are **suspected to be related** to the administration of study medication. (See Section 3.5.3: Safety assessments, for the definitions to be used in evaluating the seriousness of an adverse event and for determining the relationship of an adverse event to study medication.)
  - ◊ Record serious events **not suspected to be related** to study medication in the CRF and/or endpoint documentation.

Potentially an investigator should never have recorded a malignancy event as an AE or SAE but only as a death event or hospitalization event. However, the hospitalization CRF captured only the primary admission diagnosis (e.g., which could be "hemoptysis" or "chest pain" for an eventual lung cancer diagnosis, with the latter never captured on the CRFs):

(b) (4)

And the death form did not capture a text cause for a malignancy death but only a checkbox:

Hence for patients with new malignancies who didn't die during the study we might not know that they had a new malignancy; for those who died we might only know that they died from a malignancy but not know the cancer site (including not knowing hematologic vs. solid cancer.) Similarly, history of cancer at baseline was recorded as a checkbox for "History of Cancer within 5 years." Determining whether cancers are incident (new) or recurrent in VALIANT is impossible for many cases.

The unfortunate ambiguities in the protocol and CRFs are reflected in the data. I analyzed all relevant VALIANT AE, hospitalization, and death datasets for cancer diagnoses. The numbers of neoplasms used for the FDA M-A were 143 valsartan, 83 control. (RR 0.86.) (VALIANT had three arms with 1:1:1 randomization: valsartan alone, valsartan+captopril, and captopril alone. For the FDA M-A and these analyses "ARB" or "valsartan" references the combined valsartan alone and valsartan+captopril arms and "control" references the captopril alone arm.) The counts of patients with neoplasms in the AE datasets are virtually identical (143 valsartan, 82 control, RR 0.87) to the FDA M-A counts. The hospitalization data set identifies another 103

patients with neoplasms not included in these numbers and the death dataset identifies another 79 (55 valsartan, 24 control, RR 1.15) who died of a malignancy excluding patients with reported hematologic malignancies. Combining the AE and death neoplasms yields 198 valsartan and 106 control neoplasms, RR 0.94. Combining the AE, hospitalization, and death neoplasms (all sources) yields 248 valsartan and 134 control neoplasms, RR 0.93. Note that, while the VALIANT FDA M-A results are favorable for valsartan, the unreported cases are unfavorable.

The NDA documents neoplasms for an additional 156 patients, 70% more than those counted in the FDA M-A. All of these numbers are likely still underreporting because, as documented above, the event reporting in VALIANT did not guarantee that all malignancies were reported. The death rate was high in patients with reported neoplasms, i.e., about 44% during the study in neoplasms reported other than death only. There were 46 cases reported only as malignancy deaths. If we assume that the death rate in unreported cases is the same as the death rate in reported neoplasms, then we would expect 46/0.44 = 105 cases either reported as a malignancy death only or not reported at all such that we do not have cancer site data.

The cancer data collected in VALIANT, both regarding completeness of ascertainment and the reporting of cancer sites, are too incomplete to be valid for any cancer M-As.

Appendix 2: Documentation of the ARB and Lung Cancer Hypothesis

One internal FDA criticism of all of the ARB and cancer meta-analyses is that they are "fishing expeditions" with severe multiplicity issues as expressed in the following email message:

From: Unger, Ellis
Sent: Wednesday, September 05, 2012 2:25 PM
To: Soukup, Mat; Jagadeesh, Gowra G; Gordon, Maryann; Stockbridge, Norman L; Nguyen, Quynh M; McCloskey, Carolyn A; Andraca-Carrera, Eugenio; Zornberg, Gwen; Ton, Phuong Nina; Marciniak, Thomas; Wachter, Lori; Southworth, Mary Ross
Cc: Temple, Robert
Subject: RE: Finalized - SAFETY-935 General Review (REV-CLINICAL-03)

I attempted to attach the following comments to Norman's memo without success. (DARRTS would not accept them, presumably because there were too many characters.) I plan to place this into DARRTS in the next day or two:

I agree with Dr. Stockbridge. I also note that no analysis, or group of analyses, no matter how carefully conducted, can circumvent the multiplicity problem here.

When considering adverse events, one can always perform a meta-analysis on a group of randomized controlled studies (RCTs) with a total sample size in the tens of thousands and find statistically significant differences, so-called "signals," especially at p-values that are only barely statistically significant (i.e., p-values just less than 0.05). One has no way of knowing how many other drugs or drug groups were assessed, or how many potential safety issues were considered (e.g., cancer [and many types of cancer], myocardial infarction, stroke, diabetes, dementia, etc.). Moreover, one has no way of knowing how criteria were established to make decisions about which studies to include or exclude in the meta-analysis.

Thus, such analyses amount to post hoc "fishing expeditions;" useful for hypothesis generation, but by no means conclusive. One must be cognizant of the inherent multiplicity and inflation of Type-I error, with the potential, or even the likelihood, of finding false positives. For example, if Sipahi et al had reported ALL safety signals of interest in the 61,590 subjects, it would not have been surprising if they had found some with RR <= 0.93, the reciprocal of 1.08, i.e., suggesting that ARBs prevent some adverse event.

Finally and importantly, it is critical to recognize that performance of additional, related, analyses on the same group of RCTs, no matter how comprehensive and refined those analyses might be, does not circumvent the original multiplicity issue. They amount to "fishing" in the same "waters." Similar findings are expected; they do not "confirm" the original finding

By Dr. Unger's arguments, we could rarely have safety concerns because most safety concerns arise from *post hoc* findings, e.g., *torsades de pointes* with terfenadine, cardiac events with rofecoxib. Dr. Unger in particular should be a supporter of *post hoc* analyses rather than an opponent because, (b) (4)

(b) (4)

However, while Dr. Unger's "fishing expedition" analogy does not even apply to most safety analyses, it is completely inapplicable to the Sipahi *et al.* meta-analysis and to this review. While Sipahi *et al.* initiated their meta-analysis based on *post hoc* findings in the candesartan CHARM trials, they tested their hypothesis prospectively in the other ARB studies. My concerns with losartan and lung cancer predated Sipahi *et al.*'s observations: I noted an imbalance in lung cancers in the LIFE trial in 2002. Because it was not statistically significant and an isolated finding I did not specifically comment upon it in my review. I did include the following table in my review for future reference—and Sipahi *et al.* used the data in the table for their meta-analysis:

Table 82: Sponsor's Serious Adverse Events with Frequencies ≥ 0.5% of Patients

	Losartan (N=4605)		Atenolol (N=4588)	
	n	(%)	n	(%)
Patients with one or more adverse experiences	1715	(37.2)	1660	(36.2)
Patients with no adverse experience	2890	(62.8)	2928	(63.8)
Body as a Whole/Site Unspecified	**414**	**(9.0)**	**398**	**(8.7)**
Abdominal pain	24	(0.5)	31	(0.7)
Chest pain	21	(0.5)	26	(0.6)
Drug overdose	88	(1.9)	65	(1.4)
Inguinal hernia	29	(0.6)	28	(0.6)
Syncope	59	(1.3)	49	(1.1)
Cardiovascular System	**357**	**(7.8)**	**396**	**(8.6)**
Atrial fibrillation	96	(2.1)	93	(2.0)
Bradycardia	9	(0.2)	43	(0.9)
Deep venous thrombosis	30	(0.7)	21	(0.5)
Pulmonary embolism	18	(0.4)	25	(0.5)
Transient ischemic attack	35	(0.8)	49	(1.1)
Digestive System	**287**	**(6.2)**	**261**	**(5.7)**
Colonic malignant neoplasm	26	(0.6)	21	(0.5)
Endocrine System	**39**	**(0.8)**	**39**	**(0.9)**
Eyes, Ears, Nose, and Throat	**92**	**(2.0)**	**93**	**(2.0)**
Cataract	27	(0.6)	22	(0.5)
Hemic and Lymphatic System	**53**	**(1.2)**	**50**	**(1.1)**
Anemia	31	(0.7)	16	(0.3)
Hepatobiliary System	**107**	**(2.3)**	**79**	**(1.7)**
Cholecystitis	29	(0.6)	24	(0.5)
Cholelithiasis	51	(1.1)	46	(1.0)
Metabolism and Nutrition	**26**	**(0.6)**	**28**	**(0.6)**
Musculoskeletal System	**385**	**(8.4)**	**367**	**(8.0)**
Hip osteoarthritis	35	(0.8)	33	(0.7)
Knee osteoarthritis	33	(0.7)	16	(0.3)
Musculoskeletal chest pain	26	(0.6)	24	(0.5)
Nervous System	**122**	**(2.6)**	**124**	**(2.7)**
Vertigo	41	(0.9)	39	(0.9)
Psychiatric Disorder	**57**	**(1.2)**	**37**	**(0.8)**
Respiratory System	**189**	**(4.1)**	**193**	**(4.2)**
Lung malignant neoplasm	29	(0.6)	12	(0.3)
Pneumonia	75	(1.6)	96	(2.1)
Skin and Skin Appendages	**127**	**(2.8)**	**129**	**(2.8)**
Basal cell carcinoma	66	(1.4)	58	(1.3)
Urogenital System	**318**	**(6.9)**	**274**	**(6.0)**
Breast malignant neoplasm	37	(0.8)	36	(0.8)
Prostatic disorder	28	(0.6)	22	(0.5)
Prostatic malignant neoplasm	58	(1.3)	42	(0.9)
Although a patient may have had 2 or more serious adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.				

Note that lung malignant neoplasm SAEs as reported by the sponsor are 29:12 losartan:control , a significant imbalance. Both the Sipahi *et al.* and FDA meta-analyses used these numbers. However, not all lung cancers are reported as "lung malignant neoplasm" or as SAEs. The counts of lung cancers in LIFE in the datasets are 45:36, not statistically significant for the LIFE study alone. (Note that the differing LIFE lung cancer counts illustrate well the problems of depending upon published statistics—even from FDA reviews—for meta-analyses. One has to understand completely how the numbers were generated and their limitations in order to perform a definitive meta-analysis. Sipahi *et al.* were correct when they concluded that their findings warranted further investigation—but the FDA meta-analysis did not recognize its limitations. The differing LIFE lung cancer counts also illustrate that the counts used in this review are not always less favorable for ARBs than those used in other meta-analyses.)

When the publication of the Sipahi *et al.* meta-analysis stimulated interest in this topic and a formal response from the FDA, I communicated my observations from the LIFE study to the FDA staff responsible for the formal response in the following email messages:

From: Marciniak, Thomas
Sent: Friday, June 11, 2010 12:43 PM
To: Southworth, Mary Ross
Cc: Stockbridge, Norman L
Subject: RE: ARBs and risk of cancer

Attachments: LIFE cancers.doc

You're right, I didn't include it in my review because the signal is weak so I did not want to create a stir. I've attached what analysis logs regarding cancer stats in LIFE I have.

Tom

_____

From: Southworth, Mary Ross
Sent: Friday, June 11, 2010 12:29 PM
To: Marciniak, Thomas
Subject: RE: ARBs and risk of cancer

Was there a review of the cancer finding in the LIFE study? I have looked through the NDA and IND and am having trouble locating anything pertinent.

From: Marciniak, Thomas
Sent: Friday, June 11, 2010 10:48 AM
To: Southworth, Mary Ross; U, Khin M; Karkowsky, Abraham M
Cc: Pease-Fye, Meg; Stockbridge, Norman L; U, Khin M
Subject: RE: ARBs and risk of cancer

Losartan in the LIFE study (lung cancer if I remember correctly), although weak and there is also a weak signal for HCTZ and renal cell carcinoma. Khin knows about telmisartan.

Tom

From: Southworth, Mary Ross
Sent: Friday, June 11, 2010 10:03 AM
To: Marciniak, Thomas; U, Khin M; Karkowsky, Abraham M
Cc: Pease-Fye, Meg; Stockbridge, Norman L
Subject: ARBs and risk of cancer

We were recently informed about the impending publication of a meta-analysis about the association b/w ARBs and cancer (see below).

In investigating the background of this issue, I see that there was a cancer signal (fatal cancers) in the CHARM program and it looks like some of the more recent large ARB trials (TRANSCEND, ONTARGET) did target collection of cancer events. I imagine this was in an attempt to further investigate this signal. Do any of you have info on this--or point me to a review in which you discussed it? Thanks!

<< OLE Object: Picture (Metafile) >>
THE LANCET ONCOLOGY: PRESS RELEASE
EMBARGO: 1830H (New York time) Sunday 13 June 2010
WIDELY USED CLASS OF BLOOD PRESSURE MEDICATIONS LINKED TO INCREASED CANCER RISK

Note that I reaffirmed at the start of the FDA formal response that the signal in LIFE for losartan was an increased rate of lung cancer.

56 pages have been withheld in full immediately following this page as a duplicate copy of the "ARB Analysis Plan." This can be found in the Summary Review section under the date 12/17/14 .

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THOMAS A MARCINIAK
08/31/2012
Original version 1.0 submitted to Dr. Stockbridge on August 3, 2012.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THOMAS A MARCINIAK
12/12/2014

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THOMAS A MARCINIAK
12/17/2014

CLINICAL REVIEW

Application Type	**NDA**
Application Number(s)	**206143**
Priority or Standard	**Priority**
Submit Date(s)	**June 27, 2014**
Received Date(s)	**June 27, 2014**
PDUFA Goal Date	**February 27, 2015**
Division / Office	**DCRP/ODE-1**
Reviewer Name(s)	**Preston M. Dunnmon, M.D.** **B. Nhi Beasley, Pharm. D.**
Review Completion Date	**December 4, 2014**
Established Name	**Ivabradine**
(Proposed) Trade Name	**Corlanor**
Therapeutic Class	**Hyperpolarization-activated, Cyclic Nucleotide-gated (HCN) I_f channel Blocker**
Applicant	**Amgen Inc**

Formulation(s)	**5 mg and 7.5 mg film-coated tablets**
Dosing Regimen	**One-half (of a 5 mg tablet) to one tablet twice daily (morning and evening, taken during meals)**
Indication(s)	**To reduce the risk of cardiovascular mortality or hospitalizations for worsening heart failure in patients with chronic heart failure [redacted] with systolic dysfunction and in sinus rhythm with heart rate ≥ 70 beats per minute (bpm), [redacted] including maximally tolerated doses of beta-blockers or when beta-blocker therapy is contraindicated [redacted]**
Intended Population(s)	**Adults with chronic heart failure, [redacted] with left ventricular systolic dysfunction, in sinus rhythm and with heart rate > 70 bpm, on standard guideline-directed therapies including maximally tolerated doses of beta-blockers**

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

According to my review of the clinical data, I recommend approval of ivabradine for a two-tiered indication in Heart Failure patients with reduced Ejection Fractions (HFrEF) as follows:

- To reduce the risk of hospitalizations for worsening heart failure in patients with chronic heart failure (b) (4) with systolic dysfunction (LVEF ≤ 35%) and in sinus rhythm with baseline heart rates ≥ 75 beats per minute (bpm), (b) (4) including maximally tolerated doses of beta-blockers

- (b) (4) to reduce the risk of CV death and to reduce the risk of hospitalizations for worsening heart failure in patients with chronic heart failure (b) (4) with systolic dysfunction (LVEF ≤ 35%) and in sinus rhythm with heart rate ≥ 75 beats per minute (bpm), in combination with standard HF therapy other than beta-blockers

In the label's dosing instructions, I recommend that:

- Patients ≥ 75 years of age or any patient with baseline heart ≤ 85 bpm be initiated on the 2.5 mg BID and the dose adjusted no sooner than every two weeks to a maximum of 7.5 mg BID per the SHIFT dose adjustment algorithm based on heart rate.

- Patients with heart rates > to 85 bpm can be initiated on the 5 mg BID dose and dose adjusted per the SHIFT dose adjustment algorithm based on heart rate.

It should be noted that the benefit for reduction of hospitalization for WHF is progressively attenuated as beta-blocker dosing approaches guideline-directed target doses of beta-blockers. For CV mortality, a nominally significant improvement with ivabradine therapy is seen only in the sub-population taking no beta-blockers at all. This benefit disappears when any background beta-blocker therapy is present.

This recommendation is made on the basis of the very robust results in SHIFT, a double-blind, placebo-controlled, parallel group, multinational, multicenter cardiovascular outcomes trial, the randomized set of which included 6505 subjects randomized 1:1 between ivabradine and ivabradine placebo, with a primary endpoint of CV death and

hospitalization for worsening heart failure (WHF). The hospitalization for WHF component drove the overall composite endpoint results as described above for the indications. The p-value of SHIFT was essentially zero. There was no investigative site or clusters of sites whose data when removed would neutralize the significance of the overall trial result. Indeed, removing the two largest contributing countries' contributions to enrollment in total (Russia and Ukraine), the trial result remained statistically significant. OSI's preliminary assessments from site audits demonstrate no trial conduct issues of concern among the sites chosen for audit.

The rationale for the higher heart rate requirement for the initiation of patients with the 5mg BID dose of ivabradine is driven by an analysis of CV outcomes based on the baseline heart rates of subjects in SHIFT. Specifically, the point estimate for the hazard ratio of the ivabradine effect on the CV death component of the primary composite endpoint (PCE) in the randomized set is non-statistically but reproducibly greater than 1.0 for subjects in SHIFT whose baseline heart rates were $\leq$ 85 bpm. This occurs in the context of knowing that the primary toxicity of ivabradine is related to drug-induced bradycardia.

This priority review was enabled by the thorough, well-organized, and well-indexed nature of this large electronic submission.

.

1.2 Risk Benefit Assessment

Table 1. FDA Risk Benefit Summary Template

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	**Summary of evidence**: • Clinical manifestations of HFrEF include paroxysmal nocturnal dyspnea, orthopnea, edema, and intolerance of exercise which can be debilitating • Natural history – approximately 50% of patients diagnosed with heart failure die within five years of their diagnosis. The remaining patients live with various degrees of disability that can range from mild impairment activity to the inability to do activities of daily living without severe breathlessness, in spite of currently available optimal medical management with both drugs and devices. • A minority of HFrEF patients are candidates for cardiac transplant.	**Conclusions (implications for decision):** A serious, often disabling condition that has an overall fatality rate of about 50% over five years.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Unmet Medical Need	**Summary of evidence**: • Available medical therapies for Heart Failure with reduced Ejection Fraction (HFrEF) include angiotensin-converting enzyme (ACE) inhibitors to reduce morbidity and mortality, beta-blockers (bisoprolol, carvedilol, or controlled release/extended release metoprolol succinate) to reduce morbidity and mortality, aldosterone antagonists to reduce morbidity and mortality, hydralazine/isosorbide dinitrate for African Americans with persistently symptomatic NYHA class III-IV heart failure receiving optimal therapy with ACE inhibitors and beta-blockers to reduce morbidity and mortality, and diuretics to improve symptoms of congestion. Digoxin carries a Class IIa recommendation for HFrEF patients to decrease hospitalizations for heart failure (HF), and may be helpful when combined with beta-blockers in controlling the ventricular response to atrial fibrillation. • Available device therapies for HFrEF include the implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT) in selected patients. • Yet in the face of these available therapies, the annual incidence of HF has remained stable over the past several decades at about 650,000 new cases annually, with a prevalence of about 5.1 million persons affected, about half of which have HFrEF.[1] • Mortality remains high at about 50% over five years. • There are more than one million hospitalizations for HF every year, and the re-hospitalization rate is about 25% at one month. • As of 2010, total cost of HF care was in excess of $40 billion annually, with half of this due to hospitalizations for new or worsening HF. • The medical burden of HF is escalating due to aging of the population, improved survival after MI, and improvements in the prevention of sudden cardiac death.	**Conclusions (implications for decision):** There is a large and growing unmet medical need for the treatment of chronic heart failure, about half of which is HFrEF.
Clinical Benefit	**Summary of evidence**: (Randomized Set) [redacted]	**Conclusions (implications for decision):** The SHIFT trial was a large, double-blind, randomized, parallel group clinical trial that enrolled in excess of 6500

[1] Yancy et al, Circulation. 2013;128:e240-e327

<table>
<tr><th>Decision Factor</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td></td><td>
<table>
<tr><td>PCE</td><td>0.82</td><td><0.0001</td></tr>
<tr><td>Death-CV</td><td>0.91</td><td>0.128</td></tr>
<tr><td>Hosp-WHF</td><td>0.74</td><td><0.0001</td></tr>
<tr><td colspan="3">Secondary Efficacy Endpoints</td></tr>
<tr><td>Hosp-any</td><td>0.89</td><td>0.0027</td></tr>
<tr><td>Hosp-CV</td><td>0.85</td><td>0.0002</td></tr>
<tr><td>Death-HF</td><td>0.74</td><td>0.014</td></tr>
<tr><td>Death-any</td><td>0.90</td><td>0.092</td></tr>
<tr><td>Death-SCD</td><td>1.05</td><td>0.630</td></tr>
<tr><td>Death-Non CV</td><td>0.87</td><td>0.455</td></tr>
</table>
</td><td>people with an average follow up of about 22 months that demonstrated a profound effect on the reduction of the primary composite endpoint of CV death and hospitalization for worsening heart failure. The result of the trial was driven primarily by the hospitalization component of the primary endpoint, with a non-significant lean toward benefit in the CV mortality component of the endpoint. The subgroup of patients who were unable to take any dose of any beta-blocker demonstrated a nominally significant reduction in CV death with ivabradine therapy (see Tables 47 and 48).</td></tr>
<tr><td>Risk</td><td>Summary of evidence:
<table>
<tr><th colspan="3">SHIFT- Relative Risk of AEs in ≥ 2% of Ivabradine Treated Subjects</th></tr>
<tr><th>Adverse events</th><th>RR</th><th>(95% CI)</th></tr>
<tr><td>Arrhythmia</td><td>1.33</td><td>(1.21, 1.46)</td></tr>
<tr><td>Atrial fibrillation</td><td>1.25</td><td>(1.05, 1.49)</td></tr>
<tr><td>Bradycardia</td><td>5.31</td><td>(3.56, 7.93)</td></tr>
<tr><td>Ventricular arrhythmia</td><td>1.04</td><td>(0.87, 1.25)</td></tr>
<tr><td>PVCs (ventricular extra systoles)</td><td>1.05</td><td>(0.84, 1.32)</td></tr>
<tr><td>HR decreased</td><td>4.04</td><td>(2.93, 5.58)</td></tr>
<tr><td>Hypertension, BP increased</td><td>1.13</td><td>(0.96, 1.33)</td></tr>
<tr><td>Conduction disturbance</td><td>1.17</td><td>(0.89, 1.54)</td></tr>
<tr><td>AV block</td><td>1.18</td><td>(0.82, 1.70)</td></tr>
<tr><td>Phosphenes, visual brightness</td><td>5.08</td><td>(3.07, 8.40)</td></tr>
<tr><td>Asthenia, fatigue, malaise, weakness, narcolepsy</td><td>1.59</td><td>(1.06, 2.38)</td></tr>
</table>
</td><td>Conclusions (implications for decision):

Adverse event bradycardia is ivabradine's principle toxicity, and bradycardia may increase the occurrence of some ventricular arrhythmias. However, it is important to put this into context: heart failure death is nominally significantly decreased with ivabradine therapy, and CV death and all-cause death are both lower in the ivabradine treatment arm of SHIFT.

Lower dose initiation in patients with baseline heart rates ≤ 85 bpm may help to avoid bradycardia, and thus may help to avoid some of these rhythm-related adverse events.</td></tr>
<tr><td>Risk Management</td><td>Summary of evidence:

No REMS is proposed by the sponsor as ivabradine's initiation and management are based on standard clinical electrocardiographic assessments.</td><td>Conclusions (implications for decision):
The reviewer agrees with the sponsor that labeling can guide the safe initiation and maintenance of this product with modifications to more carefully manage patients with lower baseline heart rates. However, further assessment of the risk</td></tr>
</table>

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
		of cardiac teratogenicity will be undertaken and the need for a REMS on this basis assessed.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

Chronic heart failure due to left ventricular dysfunction, also referred to as Heart Failure with reduced Ejection Fraction (HFrEF), is substantial and growing medical problem that effects millions of adults in the United states. Class I recommendations in the 2013 ACCF/AHA guidelines for the pharmacologic treatment of HFrEF include:[2]

- Angiotensin-converting enzyme (ACE) inhibitors, or angiotensin II receptor blockers (ARBs) if ACE inhibitors are not tolerated, to reduce morbidity and mortality
- beta-blockers (bisoprolol, carvedilol, or controlled release/extended release metoprolol succinate) to reduce morbidity and mortality
- Diuretics and a low-sodium diet, if there is evidence of fluid retention to improve symptoms
- Aldosterone antagonists (provided estimated creatinine > 30 mL/min and K+ < 5.0 mEq/dL) to reduce morbidity and mortality.
- Hydralazine/isosorbide dinitrate (for African Americans with persistently symptomatic NYHA class III-IV heart failure) receiving optimal therapy with ACE inhibitors and beta-blockers, to reduce morbidity and mortality.

Digoxin carries a Class IIa recommendation in this guideline for HFrEF patients to decrease hospitalizations for heart failure (HF), and may be helpful when combined with

[2] Yancy et al, Circulation. 2013;128:e240-e327

beta-blockers in controlling the ventricular response to atrial fibrillation, which occurs commonly in HFrEF patients.

Atrial arrhythmias and ventricular arrhythmias are noted to contribute to the morbidity and mortality of HF, but most antiarrhythmics are also negative inotropes and are proarrhythmic in HFrEF patients. Amiodarone and dofetilide are the only antiarrhythmics that have demonstrated a neutral effect on mortality in HF patients. All class I antiarrhythmics, as well as the class III agents sotalol and dronedarone should be avoided in HFrEF patients.

Calcium blockers should be avoided in HFrEF patients.

In addition to the indicated pharmacotherapies for HFrEF, Class I recommendations for the device treatment of HFrEF, including the implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT), are as follows:

- ICD therapy for primary prevention of sudden cardiac death (SCD) to reduce total mortality in selected patients with nonischemic DCM or ischemic heart disease at least 40 days post-MI with LVEF of 35% or less and NYHA class II or III symptoms on chronic guideline-directed medical therapy (GDMT), who have reasonable expectation of meaningful survival for more than 1 year
- CRT for patients who have LVEF of 35% or less, sinus rhythm, left bundle-branch block (LBBB) with a QRS duration of 150 ms or greater, and NYHA class II, III, or ambulatory IV symptoms on GDMT
- ICD therapy for primary prevention of SCD to reduce total mortality in selected patients at least 40 days post-MI with LVEF of 30% or less, and NYHA class I symptoms while receiving GDMT, who have a reasonable expectation of meaningful survival for more than 1 year.

In spite of these guideline-directed medical and device therapies for HFrEF, the emergence of new treatments for this disease over recent years has been sparse, the burden of the disease on the health care system is high and growing, its death rate is high, and it is the leading cause of hospitalization and re-hospitalization in the US. The unmet medical need for new treatment options is profound.

Relevant to the development of Ivabradine, recent observational studies have demonstrated a correlation between resting heart rate (HR) in and CV outcomes (hospitalization for WHF and death) in patients with symptomatic HF, with an upward inflection of risk in patients with a resting HR $\geq$ 70 bpm. Meta-analysis of beta-blocker trials suggest that the improvement in CV outcomes with beta-blocker therapy is related to the degree of beta-blocker induced heart rate reduction. However, many patients cannot take guideline-directed doses of beta-blockers for HFrEF, cannot take beta-blockers at all, or continue to have heart rates $\geq$ 70 bpm on full dose beta-blocker. Consequently, the hypothesis that the sponsor tested in the SHIFT trial was that HR is not just a biomarker of

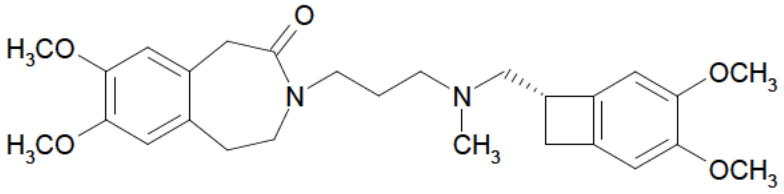
CV risk in HFrEF, [redacted] and WHF requiring hospitalization, and modifiable by a drug that can be used as add on to standard therapies to decrease HR if the resting HR is ≥ 70 bpm.

Ivabradine is thought by the sponsor to be a selective inhibitor of the cardiac pacemaker f-current (I_f), which reduces the slope of spontaneous diastolic depolarization, thereby slowing the spontaneous firing of sino-atrial node cells and reducing HR. The SHIFT trial is submitted as a single Phase 3 trial supporting for ivabradine NDA 206143 to reduce the risk of [redacted] hospitalizations for worsening heart failure in patients with chronic heart failure [redacted] with heart rate ≥ 70 beats per minute (bpm), [redacted] including maximally tolerated doses of beta-blockers or when beta-blocker therapy is contraindicated [redacted].

2.1 Product Information

- Established name (proposed trade name): Ivabradine (Corlanor)
- Chemical name: 3-(3-{[((7S)-3,4-Dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)methyl] methyl amino} propyl)-1,3,4,5-tetrahydro-7,8-dimethoxy-2H-3-benzazepin-2-one, hydrochloride
- Chemical class: new molecular entity (NME), first in class Hyperpolarization-activated, Cyclic Nucleotide-gated (HCN) I_f channel blocker with the following molecular structure:

Figure 1. Ivabradine Molecular Structure



, HCl

- Pharmacologic class: heart rate lowering agent, acting by selective inhibition of the cardiac pacemaker I_f current that controls the spontaneous diastolic depolarization in the sinus node and regulates heart rate
- Proposed indications, dosing regimens, age groups
    - Corlanor (ivabradine) is indicated to reduce the risk of cardiovascular mortality or hospitalizations for worsening heart failure in adult patients with

chronic heart failure [redacted] (b) (4) with systolic dysfunction and in sinus rhythm with heart rate ≥ 70 beats per minute (bpm), [redacted] (b) (4) including maximally tolerated doses of beta-blockers, or when beta-blocker therapy is contraindicated [redacted] (b) (4)

- The recommended starting dose of Corlanor (ivabradine) is 5 mg twice daily. After 2 weeks of treatment, if heart rate is between 50 and 60 bpm, the dose of 5 mg twice daily should be maintained. The dose should be increased to 7.5 mg twice daily if resting heart rate is persistently above 60 bpm. The dose should be decreased to 2.5 mg twice daily (one half of 5 mg tablet twice daily) if resting heart rate is persistently below 50 bpm or in case of symptoms related to bradycardia such as dizziness, fatigue, or hypotension. Treatment must be discontinued if heart rate remains below 50 bpm or symptoms of bradycardia persist after dose reduction.
- [redacted] (b) (4)
- It is recommended that Corlanor (ivabradine) be taken with meals.

- Brief Product Description: Corlanor (ivabradine) is formulated as salmon-colored, film-coated tablets for oral administration in strengths of 5 mg and 7.5 mg of ivabradine as the free base equivalent. Each IR tablet contains the active ingredient ivabradine and the following inactive ingredients: lactose monohydrate, magnesium stearate, maize starch, maltodextrin, and colloidal silicon dioxide. Additionally, the IR tablets are film-coated with glycerol, hypromellose, polyethylene glycol 6000, magnesium stearate, red iron oxide, titanium dioxide, and yellow iron oxide.

2.2 Tables of Currently Available Treatments for Proposed Indications

The commonly used class I pharmacologic agents used in HFrEF are summarized in the tables below:[3]

[3] Yancy et al, Circulation. 2013;128:e240-e327

Table 2. Oral Diuretics Recommended in the US for Treatment of Chronic HF

Drug	Initial Daily Dose(s)	Maximum Total Daily Dose	Duration of Action
Loop diuretics			
Bumetanide	0.5 to 1.0 mg once or twice	10 mg	4 to 6 h
Furosemide	20 to 40 mg once or twice	600 mg	6 to 8 h
Torsemide	10 to 20 mg once	200 mg	12 to 16 h
Thiazide diuretics			
Chlorothiazide	250 to 500 mg once or twice	1,000 mg	6 to 12 h
Chlorthalidone	12.5 to 25.0 mg once	100 mg	24 to 72 h
Hydrochlorothiazide	25 mg once or twice	200 mg	6 to 12 h
Indapamide	2.5 mg once	5 mg	36 h
Metolazone	2.5 mg once	20 mg	12 to 24 h
Potassium-sparing diuretics*			
Amiloride	5 mg once	20 mg	24 h
Spironolactone	12.5 to 25.0 mg once	50 mg†	1 to 3 h
Triamterene	50 to 75 mg twice	200 mg	7 to 9 h
Sequential nephron blockade			
Metolazone	2.5 to 10.0 mg once plus loop diuretic	N/A	N/A
Hydrochlorothiazide	25 to 100 mg once or twice plus loop diuretic	N/A	N/A
Chlorothiazide (IV)	500 to 1,000 mg once plus loop diuretic	N/A	N/A

*Eplerenone, although also a diuretic, is primarily used in chronic HF.
†Higher doses may occasionally be used with close monitoring.
HF indicates heart failure; IV, intravenous; and N/A, not applicable.

Table 3. Drugs Commonly Used in the US for Stage C HFrEF

Drug	Initial Daily Dose(s)	Maximum Dose(s)	Mean Doses Achieved in Clinical Trials
ACE inhibitors			
Captopril	6.25 mg 3 times	50 mg 3 times	122.7 mg/d (422)
Enalapril	2.5 mg twice	10 to 20 mg twice	16.6 mg/d (413)
Fosinopril	5 to 10 mg once	40 mg once	N/A
Lisinopril	2.5 to 5 mg once	20 to 40 mg once	32.5 to 35.0 mg/d (445)
Perindopril	2 mg once	8 to 16 mg once	N/A
Quinapril	5 mg twice	20 mg twice	N/A
Ramipril	1.25 to 2.5 mg once	10 mg once	N/A
Trandolapril	1 mg once	4 mg once	N/A
ARBs			
Candesartan	4 to 8 mg once	32 mg once	24 mg/d (420)
Losartan	25 to 50 mg once	50 to 150 mg once	129 mg/d (421)
Valsartan	20 to 40 mg twice	160 mg twice	254 mg/d (108)
Aldosterone antagonists			
Spironolactone	12.5 to 25.0 mg once	25 mg once or twice	26 mg/d (425)
Eplerenone	25 mg once	50 mg once	42.6 mg/d (446)
Beta blockers			
Bisoprolol	1.25 mg once	10 mg once	8.6 mg/d (117)
Carvedilol	3.125 mg twice	50 mg twice	37 mg/d (447)
Carvedilol CR	10 mg once	80 mg once	N/A
Metoprolol succinate extended release (metoprolol CR/XL)	12.5 to 25 mg once	200 mg once	159 mg/d (448)
Hydralazine and isosorbide dinitrate			
Fixed-dose combination (424)	37.5 mg hydralazine/ 20 mg isosorbide dinitrate 3 times daily	75 mg hydralazine/ 40 mg isosorbide dinitrate 3 times daily	~175 mg hydralazine/90 mg isosorbide dinitrate daily
Hydralazine and isosorbide dinitrate (449)	Hydralazine: 25 to 50 mg, 3 or 4 times daily and isosorbide dinitrate: 20 to 30 mg 3 or 4 times daily	Hydralazine: 300 mg daily in divided doses and isosorbide dinitrate 120 mg daily in divided doses	N/A

2.3 Availability of Proposed Active Ingredient in the United States

Corlanor (ivabradine) is a first-in-class NME that is not currently marketed in the US. However, as of December 2013, has been approved in 88 countries outside the United States (US) for the treatment of chronic heart failure and in 102 countries for the treatment of angina.

2.4 Important Safety Issues with Consideration to Related Drugs

FDA is unaware of the marketing or current late phase development of any other I_f channel blocker for clinical use. Negative chronotropes (drugs that slow the heart rate) in general have the potential to cause clinically significant and sometimes severe bradycardias (some due to sinus node dysfunction, and some due to AV node dysfunction), and bradycardia may increase the incidences of some types of ventricular arrhythmias (e.g. Torsade de Pointes). Combinations of negative chronotropes can be particularly problematic in this regard, particularly in older patients with a higher incidence of intrinsic conduction system disease.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The sequence of communications between the sponsor and the review division with respect to this development program is summarized below:

Date	Regulatory
11/15/2011	PIND Meeting
12/06/2013	Type B Pre-NDA meeting (CMC Only)
12/09/2013	FDA internal consult from QT-IRT regarding TQT waiver request
01/22/2014	Type C Top-line results meeting
01/23/2014	Type B Pre-NDA meeting
06/27/2014	NDA submitted
09/23 2014	Proprietary name granted
10/06/2014	Mid-cycle communication

Relevant details of the discussions at the meetings preceding this NDA filing are as follows:

November 15, 2011 PIND Meeting

- FDA met with Servier for the purpose of clarifying the information that would be required for an NDA submission for the HF indication. Specifically, Servier pointed out that all ivabradine studies were conducted under GCP but not under a US IND and asked the Division what if any information related to the conduct of the studies would be needed for these trials be the supporting basis of an NDA. The Division informed the sponsor that Under CFR 312.120 and CFR 314.106, if an application is based solely on foreign clinical data, it must (a) meet the US criteria for marketing approval, (b) show that (i) the foreign data are applicable to the US population and the US medical practice, (ii) the studies have been performed by clinical investigators of recognized competence (as described in CFR 312.120), and (c) be able to be validated by FDA through on-site inspections or other appropriate means.

In addition, the clinical trial sites must be documented to have had IRB oversight and must have retained copies of informed consent forms signed by all subjects.

- (b) (4) all marketing applications are required to include financial disclosure information or certification that the sponsor acted with due diligence to obtain the information but was unable to do so (21 CFR § 54.4). The importance of obtaining adequate financial disclosure information was emphasized.
- Asked whether study CL3-063 (SHIFT) provided sufficient evidence to support an indication for ivabradine for the reduction of cardiovascular events (b) (4) hospitalization for worsening heart failure) in patients with symptomatic systolic heart failure in sinus rhythm with a heart rate ≥70 bpm, the Division noted that the sponsor was submitting only a single clinical trial to provide evidence of safety and efficacy (instead of two), and that a trial in a similar population (BEAUTIFUL), the incidence of the composite of CV mortality, hospitalization for heart failure and hospitalization for acute MI slightly favored placebo (844 vs. 832) and more CV deaths were observed in ivabradine subjects than placebo subjects (469 vs. 435). Further, SHIFT was performed mostly in Eastern Europe (4243 subjects of 6505 total) where medical practice and available therapeutic options differ from those in the United States. Finally, the benefit of ivabradine on cardiovascular events appears to be driven mainly by a reduction in hospitalization for worsening heart failure among subjects who were not on full doses of β-blockers despite unequivocal evidence that β-blockers reduce mortality. We think it likely that if approved, ivabradine will be indicated only for heart failure patients in sinus rhythm and a heart rate ≥70 bpm despite maximally tolerated doses of β-blockers.

December 9, 2013

The QT-IRT conclusion/recommendation regarding a TQT study waiver was that, *"A TQT study is not required because we do not consider that it will adequately assess ivabradine's proarrhythmic liability due to the confounding effects of the large decrease in heart rate. Torsade de pointes cases reported in patients treated with ivabradine should be stated in the label under warning and precautions."*

January 23, 2014

- The Division communicated the expectation that the hepatic safety of ivabradine has been assessed as suggested in FDA's Guidance on drug-induced liver injury and specifically, that appropriate laboratory sampling was obtained during the ivabradine development program to perform the categorical analyses for hepatic injury that are discussed in this document. The Division noted the sponsor's remark that liver enzyme assessments from SHIFT were not systematically acquired, and communicated to the sponsor that if there was indeed no systematic assessment of

hepatic laboratory safety in SHIFT, it would be important to submit a comprehensive analysis of hepatic safety per the guidance in an appropriately integrated dataset from other trial sources.

- The Division asked for a rank analysis for all cause death with no censoring, an analysis for time to first death and all cause hospitalization, and an analysis of incomplete follow-up (i.e., the status of an event that is part of the primary endpoint is unknown).
- It was agreed that (b) (4) are not relevant to the claim, so no datasets are required, but EQ5 and KCCQ information will be submitted.
- The Division agreed that A TQT study is not required because we do not consider that it will adequately assess ivabradine's proarrhythmic liability because of the confounding effects of the large decrease in heart rate.
- The Division communicated the need to provide clinical data demonstrating the lack of withdrawal-type and rebound behavior, as well as any abuse behavior, and address the abuse potential in the NDA submission.
- A preliminary discussion on the need for REMS was held and it was concluded that a REMS is not needed.

2.6 Other Relevant Background Information

Ivabradine is approved in the European Union for the treatment of angina, as well as for the treatment of HFrEF. EMA initiated a review of the safety of ivabradine in May 2014 based on the results of the SIGNIFY study (see section 5.3.3 of this review for a summary of the design and outcome of SIGNIFY). SIGNIFY was a multi-center, randomized, double-blind, placebo-controlled, event-driven study in patients with stable coronary artery disease and sinus heart rate $\geq$ 70 bpm, without left ventricular systolic dysfunction (LV ejection fraction > 40%) and without clinical heart failure (excluded NYHA class II or higher, or hospitalization for heart failure _12 months). This study used doses of ivabradine higher than currently recommended in the EU product information (starting dose 7.5 mg twice daily, up to 10 mg twice daily). While overall SIGNIFY was neutral, a small but significant increase in the combined risk of CV death or non-fatal MI was noted in a subgroup of patients with symptomatic angina (Canadian Class II-IV) treated with ivabradine as compared to placebo (3.4% vs 2.9% yearly incidence rates). It was also noted that there was a higher risk of bradycardia with ivabradine as compared to placebo (17.9% vs. 2.1%). Atrial fibrillation also occurred more frequently in the ivabradine treatment arm as compared to placebo (4.9% vs 4.1%)

After an extensive review, the EMA published the following recommendations with respect to ivabradine's use in angina patients on November 21, 2014:

- *The data from SIGNIFY did not demonstrate a beneficial effect for Corlentor/Procoralan on cardiovascular outcomes in coronary artery patients without clinical heart failure. Its use is only beneficial for symptomatic treatment in patients with chronic stable angina pectoris who cannot be treated with beta-*

blockers, or in combination with beta-blockers in case their disease is not controlled with them alone.

- *In the symptomatic treatment of patients with chronic stable angina, Corlentor/Procoralan should only be started if the patient's resting heart rate is above or equal to 70 beats per minute (bpm).*
- *The starting dose of Corlentor/Procoralan should not exceed 5 mg twice daily and the maintenance dose of Corlentor/Procoralan should not exceed 7.5 mg twice daily.*
- *Corlentor/Procoralan should be discontinued if the symptoms of angina do not improve within 3 months. In addition, discontinuation should be considered if the improvement is only limited and if there is no clinically relevant reduction in resting heart rate within 3 months.*
- *The concomitant use of Corlentor/Procoralan with verapamil or diltiazem is now contraindicated.*
- *Prior to starting treatment or when considering titration, serial heart rate measurements, ECG, or ambulatory 24-hour monitoring should be considered when determining the heart rate.*
- *The risk of developing atrial fibrillation is increased in patients treated with Corlentor/Procoralan. Regular monitoring for the occurrence of atrial fibrillation is recommended. If atrial fibrillation develops during treatment, the balance of benefits and risks of continued Corlentor/Procoralan treatment should be carefully reconsidered.*
- *If during treatment the heart rate decreases below 50 bpm at rest or the patient experiences symptoms related to bradycardia, the dose must be decreased (the lowest dose is 2.5 mg twice daily). If, despite dose reduction, the heart rate remains below 50 bpm or symptoms of bradycardia persist, treatment must be discontinued.*

Reviewer's Comment: SIGNIFY tested a higher dose of ivabradine as compared to SHIFT (mean dose 8.2±1.7 mg BID versus 6.4±1.4 mg BID, respectively) in a different population of patients (stable coronary artery disease and sinus heart rate ≥ 70 bpm, without left ventricular systolic dysfunction (mean LVEF 56%) and without clinical heart failure (excluded NYHA class II or higher, or hospitalization for heart failure in the prior 12 months). Accordingly, more patients experienced AE bradycardia during SIGNIFY (18% versus 2% for ivabradine and placebo respectively in SIGNIFY, whereas for SHIFT, 10.1% versus 2.3% of ivabradine and placebo patients, respectively, experienced AE bradycardia). The recommendations of the EMA in this public announcement align dosing levels, resting heart rate requirements, and the exclusion of concomitant non-DHP CCBs with what was done in the SHIFT trial in HFrEF patients.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This was a large submission with alphanumeric file designations that were initially challenging to deconstruct. However, as with any indexing system, the file structure became very intuitive as we worked with it, and the information that was contained in the various files and folders was exceptionally well organized. All hyperlinking was functional. Though SIGNIFY datasets were requested early in the review cycle, they did not arrive at FDA until several weeks before the due date of the clinical review.

3.2 Compliance with Good Clinical Practices

With respect to all Phase 2 and Phase 3 studies submitted to support this NDA, the sponsor states that, *All (Phase 2 and Phase 3) studies complied with Good Clinical Practice (GCP) in accordance with International Conference on Harmonization (ICH) E6. Ivabradine clinical studies were performed by clinical investigators of recognized competence. All study centers had oversight from Institutional Ethics Committees and copies of informed consent forms from all subjects have been retained. Essential study documents were retained by the sites and sponsor as appropriate. Study centers are available for on-site inspection or other appropriate means of validation.*

3.3 Financial Disclosures

SHIFT was conducted completely outside the US, not under an IND. It was completed on April 19, 2010. Accordingly, collection of Certification/Disclosure Forms in compliance with 21 CFR Part 54 was not prospectively acquired. In April 2012, 2 years after the completion of SHIFT, Servier initiated the collection of the US required Certification/Disclosure Forms in anticipation of a US NDA filing for a CHF indication. The response rate from the investigators to the retrospective requests was predictably poor, as shown in the table below:

Table 4. SHIFT Disclosure Categories, Sites, and Patients

Disclosure Category	**# of Sites (%)**	**# of patients**
Disclosed Interests	14 (2.1)	208
Disclosed No Interests	314 (46.4)	2838
Did not respond	349 (51.6)	3511
Total	667	6505

We note that 667 sites in total were approached for this information, the sites that enrolled the 6505 patients of the randomized set that was defined as excluding the two Polish sites whose data was excluded due to site misconduct. Thus, 52% of sites did not provide financial disclosure information, and these non-responsive sites enrolled 54% of the randomized set (RS).

This low response rate occurred in spite of the sponsor's attestation that "…all reasonable effort and due diligence was made by Servier to obtain the disclosure of financial arrangements and/or interests". These efforts included the following:

- Reminders send via email directly to the PI and co-investigators following the initial request sent via courier
- Email reminders sent to their in country representatives to continue collecting outstanding financial disclosures in June 2012, November 2012, January 2013, and July 2013
- In country representative follow-up directly with the investigators via email, telephone, or during visits to the clinical center to collect outstanding information.

To minimize the potential for bias created by disclosable financial interests and/or arrangements, Servier employed the following steps to minimize bias of the clinical study results by any of the disclosed arrangements or interests:

- Multiple clinical sites were used
- The study was blinded
- Clinical site monitoring
- Independent and centralized assessment of Endpoints and Safety
- Servier is not a publicly traded company thus no equity interest in the company existed for its Investigators

- Members of the Executive Committee, Data Monitoring Committee (DMC) and Endpoint Validation Committee (EVC) were restricted to individuals free of apparent significant conflicts of interest
- DMC members were not Investigators
- EVC members who were Investigators did not preside over the adjudication of Endpoints for subjects at their site, and for subjects at sites within their country (if they were National Coordinators).

Table 5. FDA SHIFT Financial Disclosure Analysis: SHIFT (CL3-16257-063)

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from applicant)
Total number of investigators identified: 667		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None.		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 14 investigators reported disclosable financial interests. 314 investigators disclosed no financial interests. 349 investigators did not respond to the disclosure information request (see detailed explanation below).		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 3 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: None. Significant equity interest held by investigator in sponsor of covered study: None.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 349		
Is an attachment provided with the reason:	Yes X	No ☐ (Request explanation from applicant)

Reviewer's comment: a majority of investigators did not respond to requests for financial disclosures. These non-responsive sites enrolled the majority of the subjects. To assess the potential for systemic bias caused by the non-disclosing sites, sites were divided into the following three groups for a forest plot analysis of SHIFT outcomes:

- *Sites that responded with nothing to disclose*
- *Sites that responded with financial disclosures*
- *Sites that did not respond.*

The following three plots show the results of these subgroup analyses for the primary composite endpoint (PCE) of SHIFT (CV death and hospitalization for WHF), as well for the two components of the PCE:

Figure 2. FDA SHIFT Analysis: Primary Composite Endpoint by Financial Disclosure Status

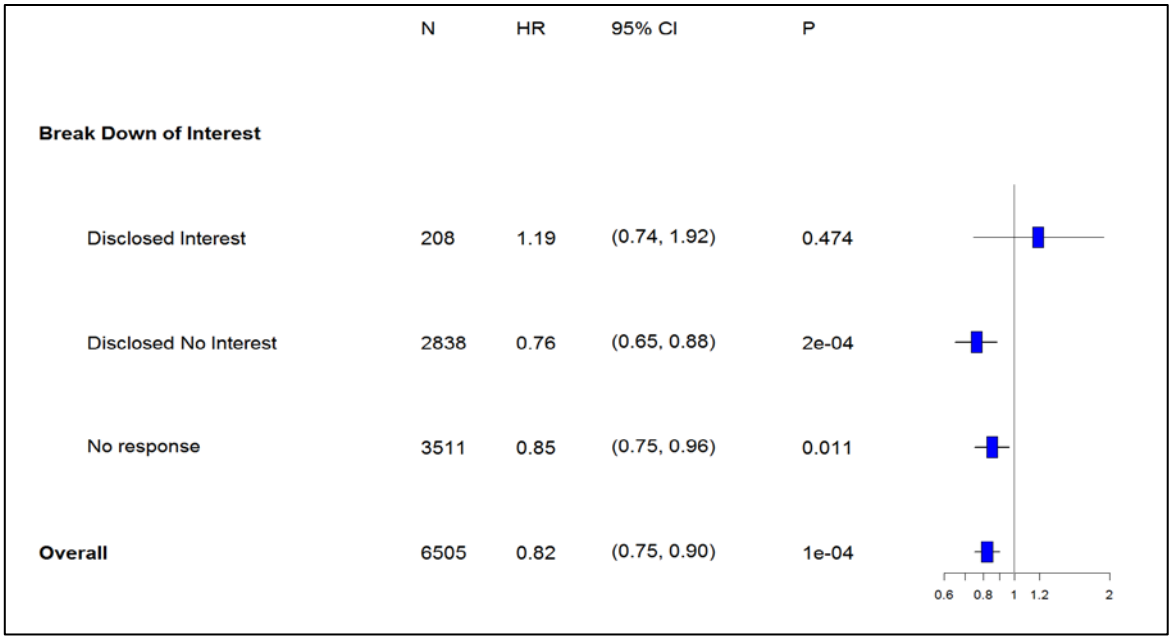


Figure 3. FDA SHIFT Analysis: CV Death by Financial Disclosure Status

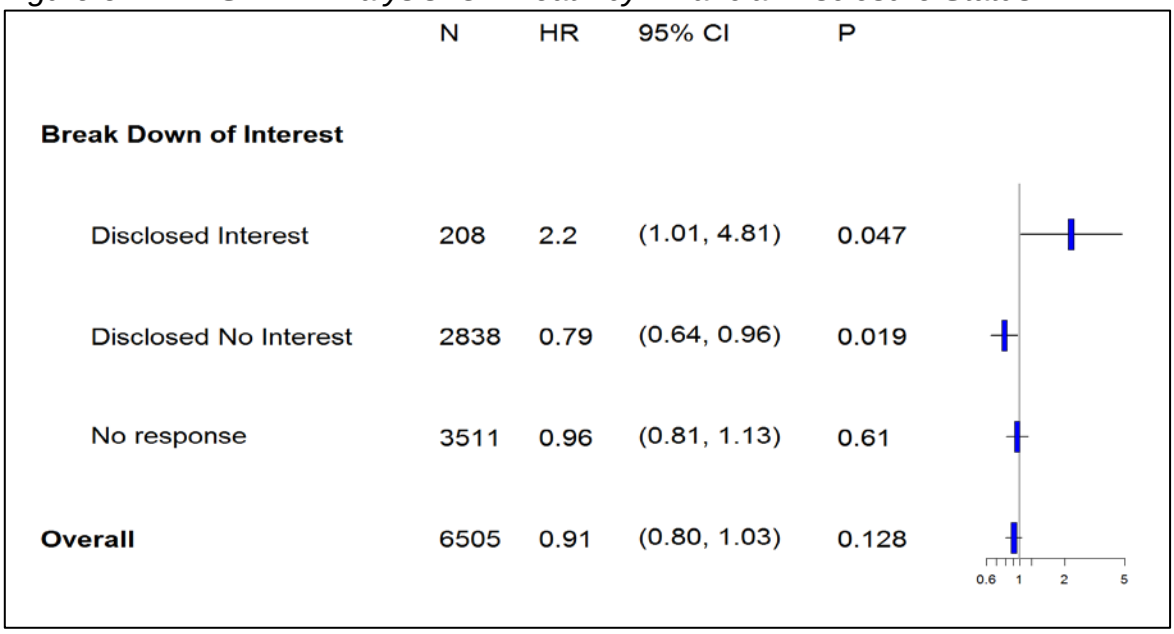
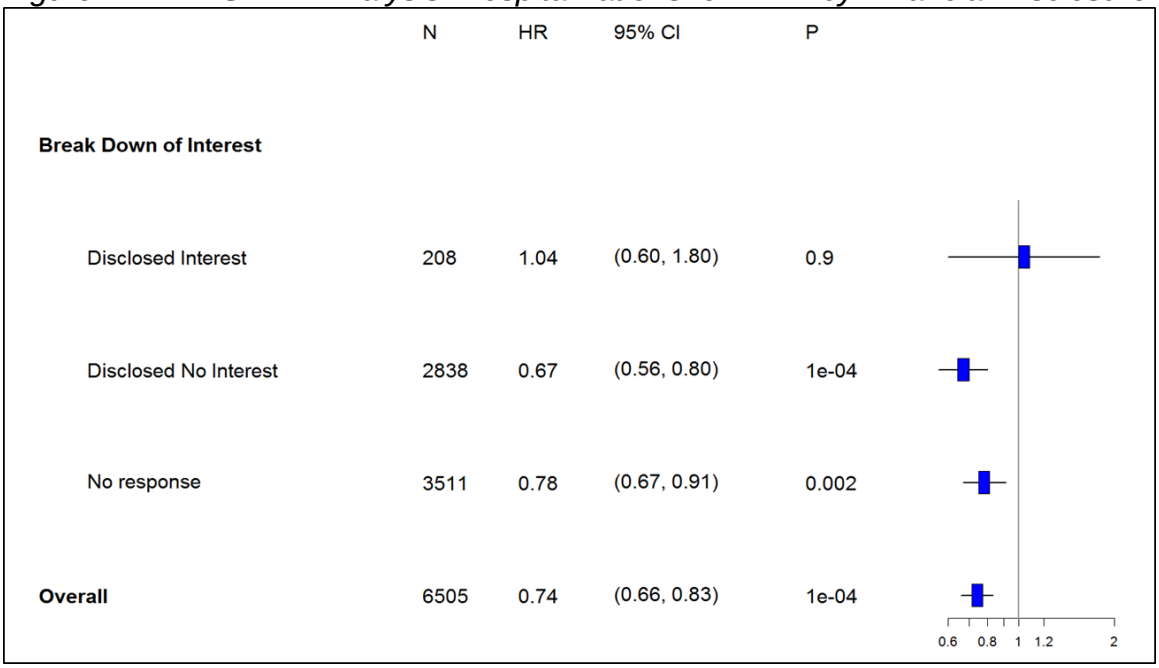


Figure 4. FDA SHIFT Analysis: Hospitalizations for WHF by Financial Disclosure Status



Reviewer's Comment: Most of the financial disclosures involved committee activity, consulting fees, or speaker's fees. However, in two instances, large payments were made to CROs that were managing or monitoring SHIFT, whose executive staff included investigators in SHIFT (i.e., these two investigators did not receive these large sums directly – the money was paid to the CROs for work performed). Combined, these two investigators who, were also CRO directors, enrolled only (b) (6) *subjects in SHIFT. However, the systemic influence these two individuals could have had on the trial is unclear. The potential for conflict of interest here occurs in the setting where SHIFT may have been partially unblinded by the negative chronotropic effect of the drug that would have been easily measurable with the acquisition of vital signs in the clinic, and the overall outcome of the trial was driven predominantly by the hospitalization component of the composite endpoint. However, I agree that the mitigation steps that Servier incorporated into the trial's management would make a systemic effect by these two individuals very unlikely, and the fact that there was a lean toward benefit in CV mortality is supportive of the lack of systemic bias in the hospitalization component of the primary composite endpoint. It is DCRP's conclusion that the passage of time was responsible for the low response rates of investigators to the requests for financial disclosure information, that the sponsor did indeed make extensive and credible efforts to obtain this information, and that the missing financial disclosure information from SHIFT should not impact the approvability of this application.*

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

CMC evaluation is in progress at the time of this review, but no significant CMC issues were noted at the time of our midcycle communication with the sponsor on 10/06/2014. See the final CMC review for this NDA.

4.2 Clinical Microbiology

Per the OPS/New Drug Microbiology review, The Microbial Limits specification for Ivabradine (Immediate Release Tablet) is acceptable from a Product Quality Microbiology perspective. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.

4.3 Preclinical Pharmacology/Toxicology

Genotoxicity and Carcinogenicity

The results of the genotoxicity assays are summarized in the following table (from FDA Pharmacology/Toxicology Genetic Toxicology Evaluation, p.40):

Table 6. FDA Summary Table of Genotoxicity Assays

Assay	+/- S9	Concentration/Dose Range[c] (µg/mL)	Results	[a]Multiples of *h*C_{max}
In Vitro assays				
Ames test	+/-	0, 46, 139, 464, 928, 1392, 2320, 4640 µg/plate	Negative	
Chromosomal Aberration in human lymphocytes	-	46*, 79, 116, 139	Equivocal	1,500*-4,500
	+	260, 487*, 882*, 1670, 2088	Negative	8,000-67,000
tk-gene mutation MLA (NP05144)	-	87 to 928*, 1160	Positive	2,800-30,000*
	+	87 to 1624	negative	2,800-52,000
tk-gene mutation MLA (NP05489)	-	116 to 1856	negative	5,200-60,000
	+	58 to 464*, 928*,1160*,1392	Positive (Inconclusive)	1,900-15,000*
UDS in rat hepatocytes	n/a	0, 55, 100, 180, 300, 400, 550*	Positive	1,800-18,000*
In Vivo assays (single dose by oral gavage)				
Micronucleus, mouse	n/a	0, 116, 232, 464 mg/kg	Negative	No TK data
Chromosomal Aberration, rat	n/a	M: 0, 232, 464, 928 mg/kg F: 0, 151, 302, 603 mg/kg	Negative	M: 294[b]; F: 581[b]
UDS, rat	n/a	M: 0, 278, 928 mg/kg F: 0, 181, 603 mg/kg	Negative	M: 110[b]; F: 203[b]

a. *h*Cmax = mean plasma maximum concentration at steady state in patients at the highest therapeutic dose of 7.5 mg bid = 31 ng/mL.
b. Multiples of hCmax were based on the mean Cmax from TK analysis in each rat study.
c. Ivabradine doses were expressed in terms of free base in this table, which could be calculated from dose of ivabradine hydrochloride × 0.928 (conversion factor).
+/-: with/without exogenous metabolic activation (rat liver S9 mix);
* indicated that a significant finding was observed at that dose (exposure) level.

The conclusions of the FDA toxicology reviewers with respect to genotoxicity and carcinogenicity are as follows:

- Ivabradine did not result in gene mutation in bacteria in vitro but was associated with a weak induction of unscheduled DNA synthesis in primary rat hepatocytes ex vivo and a weak induction of *tk* gene mutation in mouse lymphoma cells in vitro.
- The genotoxic responses were observed at dose concentrations > 15,000 fold of human Cmax at maximum recommended human dose (MRHD), 7.5 mg bid, in these assays.
- The chromosomal aberration test in human lymphocytes produced an equivocal result for a possible weak clastogenic activity due to lack of dose-dependency.
- In vivo, ivabradine did not show genotoxicity in three separate tests in mice and rats.
- The negative results were achieved at dosages up to 464 mg/kg (base) in the mouse micronucleus test and at plasma exposures > 100 fold of human Cmax at MRHD in the rat chromosome aberrations test and the rat liver UDS assay.

- Given the uniformly negative in vivo results, the weak in vitro genotoxic responses observed at concentrations about 15,000 fold of human Cmax, ivabradine is unlikely to pose a genotoxic risk in the proposed clinical use. The conclusion is substantiated by the results of 2-year carcinogenicity studies in rats and mice which showed no evidence of tumorogenic potential after dietary administration of ivabradine at dosages up to 120/60 mg/kg/day (rats) and 405/180 mg/kg/day (mice), respectively.

Reproductive and Postnatal Development Effects

The sponsor reports the following repro-developmental findings (from the sponsor's toxicology written summary):

- *When pregnant animals were treated during organogenesis at exposures close to therapeutic doses at HTD (1-3x), there was a higher incidence of fetuses with cardiac teratogenicity characterized by abnormal shape of the heart with anomalies of the major proximal arteries in the rat; and reduced embryo-fetal survival in rabbits. A small number of fetuses with ectrodactylia in the rabbit were observed at exposures 15-30 times higher than therapeutic doses at HTD*
- *In juvenile rats, the toxicological profile of ivabradine was the same as that noted in mature animals, with the heart being the main target organ. Furthermore, there was no effect on the postnatal development and on the reproductive performance.*

General Toxicology

The sponsor reports that on- target effects in the heart were the main toxicity findings in both animal species (dog and rodents) as follows (from the sponsor's toxicology written summary):

- *In rodents, high doses and/or long-term administration of ivabradine were associated with an exacerbation of spontaneously occurring myocardial lesions. In the absence of similar findings in dogs treated with ivabradine, and since such cardiac changes in rats appear to be common to heart-rate reducing agents, i.e. β-blockers, this finding can be related to the sustained and particularly extensive heart-rate reduction (HRR) induced by ivabradine in rodents, that is not reached in dogs or humans which have a much lower basal heart rate.*
- *In dogs, high plasma Cmax of ivabradine were sometimes associated with ECG changes, characterized by sinus bradycardia, sinoatrial block or arrest and first- or second-degree atrioventricular block; this was consistent with an exaggerated pharmacology of ivabradine in this animal species with a high vagal tone.*

As a consequence of I_h channel blockade in the eye (another HCN channel) visual symptoms reported during clinical trials prompted extensive ophthalmology evaluations in

animals that included electroretinography (ERG) in the one-year dog study with the following findings (from the sponsor's toxicology written summary):

- *Results showed that ivabradine induced ERG changes, mainly in the cone system responses, that were fully and rapidly reversed upon treatment cessation. Furthermore, there were no histological or ultrastructural changes in the eye sections of these dogs up to mean plasma AUC_{24} 50-fold higher than in patients at HTD. Altogether, these findings fully support the absence of neuroretinal degeneration, and point to a pure pharmacological side-effect that could be expected at high doses of the I_f (HCN) blocker ivabradine, since HCN ion channels belonging to the same family and sharing common properties are present in the retina, as well as in the heart.*

The sponsor also noted the following effects in other organ systems:

- *In dogs and rodents, neuromuscular signs associated with high plasma Cmax, and convulsions at very high doses (Cmax at least ~105-fold greater than in patients)*
- *Increased water diuresis or sodium urinary excretion was occasionally observed in rats, but not in dogs. Effects appear secondary to the sustained and extensive HRR in rats, associated with increased mechanical stress on atria and subsequent release in plasma of ANP*
- *In dogs, thymus atrophy was occasionally noted after once daily repeated dosing with ivabradine. Since comprehensive examination showed no sign of immunosuppression (including hematology, lymphoid tissues microscopic examination, bone marrow cellularity, animals health status, as well as lack of immunotoxicity potential in rats), such effect was more likely a nonspecific consequence of stress in these animals.*
- *Reduced body-weight gain across species, generally associated with decreased food consumption, increased liver weight and/or liver function tests in rodents in the absence of cytochrome P450 induction, and*
- *Increased plasma lipids in rats.*

Of note, the sponsor reports lack of demonstrable immunotoxic effects in a dedicated 4-week rat study. For details of reproductive and general toxicology findings, see the FDA pharmacology/toxicology review.

4.4 Clinical Pharmacology

See the FDA clinical pharmacology review for details.

4.4.1 Mechanism of Action

The I_f, or "funny current", is a mixed sodium-potassium current that activates during diastolic transmembrane hyperpolarization. cAMP binding to HCN4 or f-channels in the

heart shifts their activation range to more positive voltages. These cyclic nucleotide-gated ion channels (CNGs) are also involved in vision and olfaction.

The intrinsic firing rate of the SA node is predominantly determined by hyperpolarization-activated (I_f), delayed-rectifier potassium (I_K), T- and L-type calcium ($I_{Ca,L}$ and $I_{Ca,T}$), and acetylcholine-activated channel currents.[4] The sponsor's patch clamping studies demonstrate that the heart-rate-reducing (HRR) activity of ivabradine is the result of a selective, dose-dependent decrease in the conductance of the HCN4 I_f, as shown in the table below in Rabbit SAN cells (from the sponsor's written pharmacology summary, pg 29):

Table 7. Effects of ivabradine on I_f, $I_{Ca,T}$, and I_k in Rabbit SAN Cells

	% of control current amplitude			
[ivabradine] (μM)	**I_f**	**$I_{Ca,T}$**	**$I_{Ca,L}$**	**I_K**
1	32±3	-	-	-
3	59±2	-	0	0
10	80±2	0	18±1	16±1

Values are mean ± SEM; n=8 to 12 -: not determined

I_f block demonstrates rate/use dependence, and similarly reduced I_f in both cell-attached and inside-out macro-patch configurations indicating a direct interaction with f-channels from the inside of the cell.

Thus, the sponsor concludes that, "*Overall, ivabradine up to 3 μM selectively inhibits I_f. No effects are observed on delayed potassium (IK), L-type and T-type calcium currents (ICa,L and ICa,T) at 3 μM. Ivabradine directly inhibits I_f in a concentration- and use-dependent manner from the intracellular side, with an apparent IC50 in the range of 2 to 3 μM.*"

Regarding the currently known isoforms of the HCN channel, the sponsor notes:

- *Four different members of the HCN family (HCN1-4) have been identified, cloned, and, when expressed functionally, they display the typical properties of native pacemaker currents (Kaupp, 2001; Biel, 2002). In mammalian cells, HCN4 is the predominant subtype in the sinoatrial node, with much lower levels of HCN1 and 2 (Shi, 1999; Moosmang, 2001).*
- *Ivabradine caused a reduction of the current amplitude of both hHCN4 and mHCN1, as for native channels (IC50 = 2.0 for HCN4 and 0.93 μM for HCN1). However, the*

1. Nof, E, Antzelevitch C, Glikson M. The Contribution of HCN4 to Normal Sinus Node Function in Humans and Animal Models. Pacing Clin Electrophysiol. Jan 2010;33(1): 100-106.

block of hHCN4 and mHCN1 with ivabradine was not identical. HCN4 block occurred only when hHCN4 channels were open, whereas for mHCN1 ivabradine reached its site of action also when the channel was closed, although less easily.

- *Binding/unbinding reactions were not allowed when channels are open, and the current flow did not affect the drug-channel interaction*
- *Ivabradine also reduced the current amplitude of hHCN2 channels in a time- and concentration-dependent fashion without affecting the voltage-dependence or the kinetics of channels activation and showed in this set of experiment a 2.8-fold higher affinity for hHCN4 than for hHCN2 (IC50 = 3.6 ± 0.4 µM and 10.2 ± 1.1 µM, respectively, p<0.05).*

4.4.2 Pharmacodynamics

In rodent hemodynamic studies, ivabradine's negative chronotropic effect predominated over its positive effect on stroke volume to produce a drop in cardiac index, as shown below for single IV doses of ivabradine (from sponsor's written summary of pharmacology p46):

Table 8. Hemodynamic Effects of Single-dose IV Ivabradine in Conscious Rats

% change vs. pre-drug over 1 h post-dose	Vehicle	ivabradine	
		1 mg/kg iv	10 mg/kg iv
Heart rate	-3±1	-33±2*	-57±9*
MBP	-3±1	-8±1*	-19±3*
Cardiac Index	-3±1	-18±1*	-41±2*
Stroke Index	-2±1	+21±2*	+32±3*
Peak aortic flow	-2±1	+4±1*	+8±1*
dF/dt_{max}	-3±1	+2±2*	+6±2*
Total peripheral conductance	+4±1	-10±1*	-28±2*
Central venous pressure	-9±3	+9±2*	+49±8*

Values are mean ± SEM; n=9 *: p<0.05 vs. vehicle

Anesthetized open-chest pigs receiving multiple doses of ivabradine demonstrate this same predominant effect of heart rate on cardiac output, as shown in the following table (from sponsor's written summary of pharmacology p48):

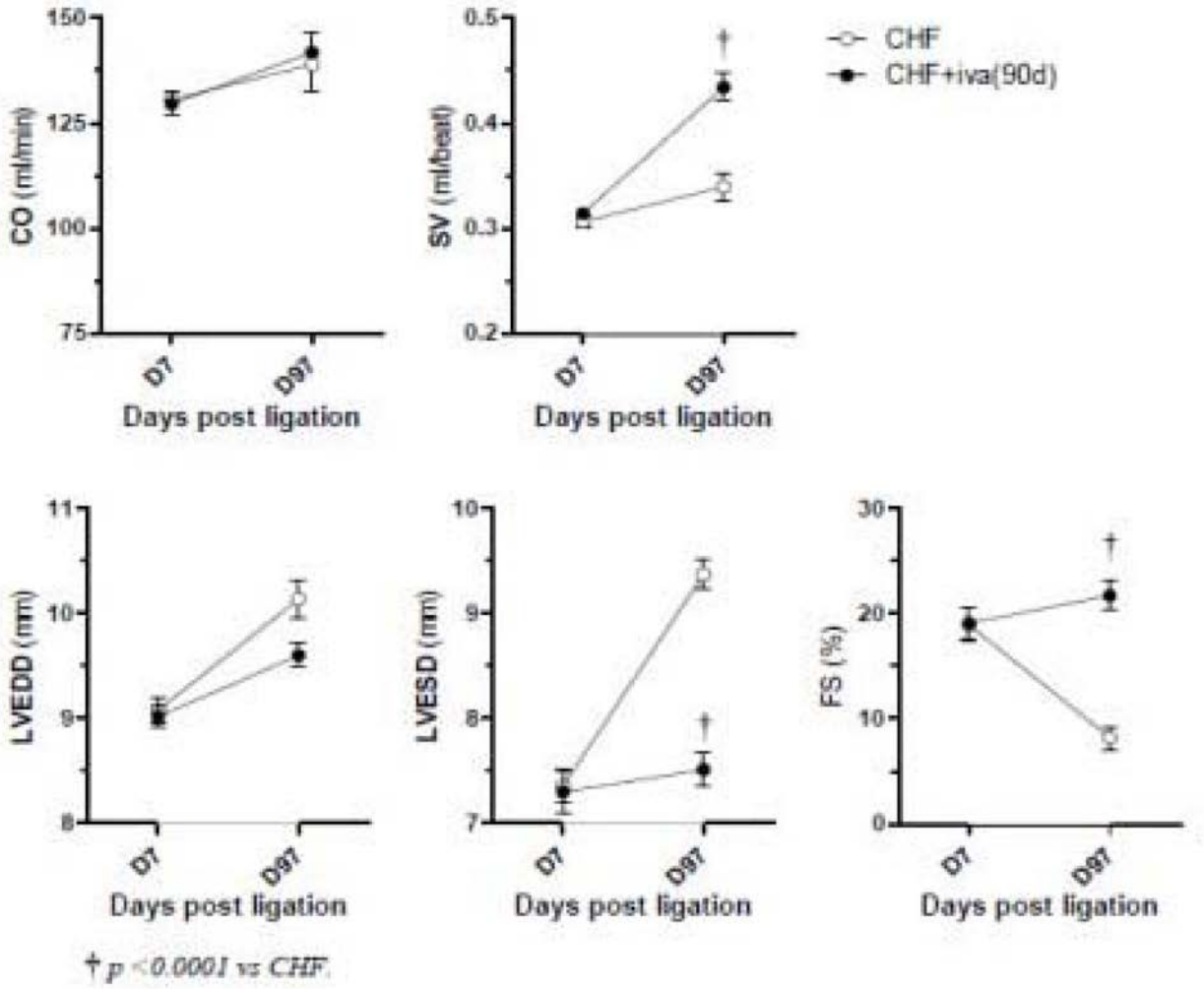
Table 9. Effects of Increasing IV doses of Ivabradine on ECG, Hemodynamic and Blood Gas Parameters in Anesthetized Pigs 20 Minutes after Each Dosing

	Mean % changes (vs. pre-drug)							
	Vehicle				ivabradine (mg/kg, iv)			
	1st iv	2nd iv	3rd iv	4th iv	0.03	0.1	0.3	1
Heart rate	-0.1	+1.0	+4.4	+3.5	-6.2	-14.1**	-23.5**	-29.3**
Mean blood pressure	+4.8	+4.6	+8.2	+9.2	+4.0	+4.1	-3.5	-5.5
LVdP/dt	-3.0	-9.3	-13.8	-20.2	-10.1	-17.4	-23.7	-28.5
Cardiac output	-2.0	-7.5	-9.3	-14.3	-8.4	-17.7	-23.8*	-28.3*
Stroke volume	-1.8	-8.1	-11.9	-16.8	-3.4	-3.4	+0.4	+2.7
Total peripheral resistance	+7.6	+13.8	+20.6	+28.7	+11.1	+22.8	+24.1	+28.9
Mean coronary vascular resistance	+10.6	+20.0	+28.2	+44.3	+9.4	+23.6	+33.8	+54.8
Myocardial oxygen consumption	+3.4	+6.4	-0.9	-4.5	-1.5	-11.7*	-21.4*	-31.6*
O_2 delivery / MVO_2 ratio	-1.8	-4.2	-4.6	-7.6	-2.6	-3.4	-5.2	-7.2

n=7-10 *: p≤0.05, **: p≤0.01 vs. vehicle

However, in a coronary ligation model of heart failure in rats receiving 10 mg/kg/day of ivabradine, day 90 assessment by echocardiography showed that cardiac output was preserved with increased stroke volume, while LVESD and LVEDD decreased compared to non-treated controls:

Figure 5. Cardiac Output, Stoke Volume and LV Diameters in CHF Rats after 90 Days Treatment



These improvements in LV geometry were accompanied by a 12% reduction of LV collagen density suggesting an anti-remodeling effect of ivabradine in this model.

In dogs following microembolizations to the circumflex and LAD targeting ejection fractions of 30-40%, apotosis was decreased, and pro-inflammatory cytokines, norepinephrine, natriuretic peptides, and RAAS proteins were decreased by ivabradine therapy, per the table below:

Table 10. Effect of Ivabradine on Circulating Biomarkers in Dog Model of HF

criteria	ACE (ng/ml)	ALDO (pg/ml)	A-II (pg/ml)	IL-6 (pg/ml)	TNF-α (pg/ml)	NE (pg/ml)	NT-proBNP (fmol/ml)	Pro-ANF (fmol/ml)
Pre-treat.	31±4	3530±525	225± 48	71±13	3.03±0.91	833±293	216±40	0.37±0.13
Iva 30 mg/kg	22±4*	1813±652*	93±31*	45±14*	1.21±0.57*	465±189*	72±26*	0.14±0.04*
% of change at 3 mo vs. pre-treat	-30	-49	-59	-37	-60	-44	-67	-62

*p<0.05 vs. pre-treatment; mo: month; pre-treat: pre-treatment

Other relevant cardiovascular PD observations include:

- The main uncleaved metabolite in human plasma, S 18982, inhibits I_f with a similar potency but slower action than ivabradine. Two additional uncleaved metabolites, Y 1016 and Y 1021, each reduced atrial beating rate with a similar potency as ivabradine.
- In conscious mongrel dogs ivabradine is a potent and specific HR lowering agent and, in contrast to propranolol, devoid of inotropic effect at rest and during treadmill exercise.
- In treadmill-exercising animals (pigs and dogs), ivabradine efficiently limits exercise-induced tachycardia and preserves the adaptations of myocardial contractility, cardiac output, mean coronary blood flow velocity, and coronary and total peripheral vascular resistances observed during exercise.
- In conscious mongrel dogs ivabradine preserves the exercise-induced acceleration of the rate of LV isovolumic relaxation, while atenolol, at similar HRR, markedly decreased the rate and extent of LV relaxation process, both at rest and during exercise (negative lusitropic effect).
- In pig and dog experimental models that mimic exercise-induced angina pectoris in humans, ivabradine significantly limits myocardial ischemia as assessed by ST-segment shift and regional myocardial contractility in the ischemic zone. Under the same conditions, and at doses inducing similar HRR, beta-blockers also effectively limit myocardial ischemia.
- In a ventricular fibrillation model in anesthetized open-chest pigs with ischemia induced at 15 min intervals, HRR induced by ivabradine protects against ventricular fibrillation by increasing the thresholds for ventricular fibrillation without negative inotropic effect and also prevents myocardial ultrastructural damage in this model.
- In a dog model of exercise-induced myocardial ischemia, the specific HR reducing activity of ivabradine affords cardioprotection against myocardial stunning by limiting exercise-induced ischemia and by improving the contractility of the stunned myocardium. By comparison, atenolol has comparable anti-ischemic properties but

worsens the contractile performance of the stunned myocardium through its negative inotropic and lusitropic effects.

- Specific chronic HRR in spontaneously hypertensive rats improves the mechanical properties of the carotid artery wall. This improvement is due to a decrease in wall stress induced by an eccentric remodeling process, i.e. a decreased carotid lumen cross-sectional area without changes of the medial thickness.
- Ivabradine does not bind to major plasma membrane receptors and binding sites, and shows some affinity for the phenyl-alkyl-amine binding site of the L-type calcium channel and for the site 2 of the voltage-dependent sodium channel
- From 3 to 10 µM, ivabradine and S 18982-1 inhibited IKr (hERG assay), with no effect on IKs (at 3 µM). Based on its hERG potency, ivabradine has a wide margin of safety (e.g., > 200-fold) relative to clinically efficacious plasma levels in patients
- In paced guinea-pig papillary muscle, and rabbit and dog purkinje fibers ivabradine has a moderate, although significant, prolonging effect on APD in these cardiac tissues when paced at very low frequency. In rabbit Purkinje fibers, paced at very low frequency (15 ppm), ivabradine-induced APD prolongation remains moderate at the highest dose (10 µM), and early after-depolarization (EAD) was not observed. In dog Purkinje fibers, the main active metabolite S 18982 shares a similar electrophysiological profile as ivabradine, with a tendency, at higher concentrations to increase APD (APD70 and APD90) at very slow rates (20 and 12 ppm).
- Oral administration of ivabradine to beagle dogs at 0.5, 1.5, 5 and 15 mg/kg twice daily for 5 days is associated with mean plasma Cmax up to 2-, 13-, 51- and 134-fold, respectively, that in patients at HTD. At all doses, a specific HRR is observed without changes in MBP, DBP or ECG parameters (including PR-interval, QRS-complex duration and QTc).
- Ivabradine can rapidly reverse dobutamine-induced tachycardia, without impairing the positive inotropic effect of the beta-adrenergic stimulation. Furthermore, this effect occurs while maintaining cardiac output, despite heart rate reduction, due to an increased stroke volume. There was no effect on PR and QT intervals other than that related to changes in heart rate.
- HRR induced by an overdose of ivabradine, associated with mean plasma levels 178-fold higher than the mean plasma Cmax in patients at HTD, can be easily reversed with either isoprenaline or dobutamine. The efficacy of atropine is less consistent than the other two agents.

PD observations relevant to the ophthalmology/visual system include:

- Ivabradine concentrations up to 10 µM (i.e. more than 100-fold the plasma Cmax in patients at HTD) for 72-hours, has no effect on the permeability barrier function of RPE cell monolayers and the integrity of RPE tight junctions
- Oral administration of ivabradine for 4 weeks to Wistar rats at a pharmacological (6 mg/kg/d) or a toxicological dose (60 mg/kg/d), showed no evidence of apoptosis or cell damage, and normal ultrastructural morphology is observed in all retinal cell layers

- Oral administration of ivabradine up to 5 days to Wistar rats at 5.6 mg/kg/d has no effect on the expression of the main effectors of the phototransduction cascade (i.e. rhodopsin, arrestin and transducin) and their regulation during adaptation to light or to dark
- Immunodetection of HCN isoforms in mouse retinal cell layers: Only HCN1 was identified in the inner segment of mouse rods, and both HCN1 and HCN2 were detected in post-synaptic neurons such as bipolar cells.
- In isolated mouse rods, ivabradine inhibits Ih (IC50~ 3 µM) and has no effect on other ionic currents, including IKx. In isolated retina, using light as a more physiologically relevant stimuli than patch-clamp, ivabradine reduces the temporal response of the retina (IC50 = 30 µM), which is consistent with an effect on I_h
- The effect of acute and chronic administration of ivabradine on the electroretinographic (ERG) response is small and reversible and restricted to very few numbers of parameters in pigmented and albino rats. The decrease in the ERG response is revealed by the harmonic analysis of responses to periodic stimuli whose mean luminance is modulated sinusoidally with no marked differences between the two strains. In pigmented rats, melanin binding was not associated with a deleterious visual effect, despite a much higher concentration of ivabradine in eye of pigmented rats as previously reported (NP08034). It is proposed that it is instead a result of a buffering action of melanin. The ERG effects are consistent with a partial I_h inhibition by ivabradine and may explain the occurrence of visual symptoms observed clinically
- Ten days of treatment with 12 mg/kg/day ivabradine induces a marked HRR, but does not affect morphology or retinal specific proteins expression in either WT or Rd10 mutant mice. It is presumed that ivabradine has no influence on the retinal degenerative processes
- Three studies were conducted to specifically evaluate potential central effects of ivabradine. In Wistar rats, after single oral doses up to 80 mg/kg/d ivabradine did not affect spontaneous locomotor activity or hexobarbital-induced sleeping time, and there was no evidence of pro-convulsant, pro-algesic or analgesic activity, or behavioral effects.

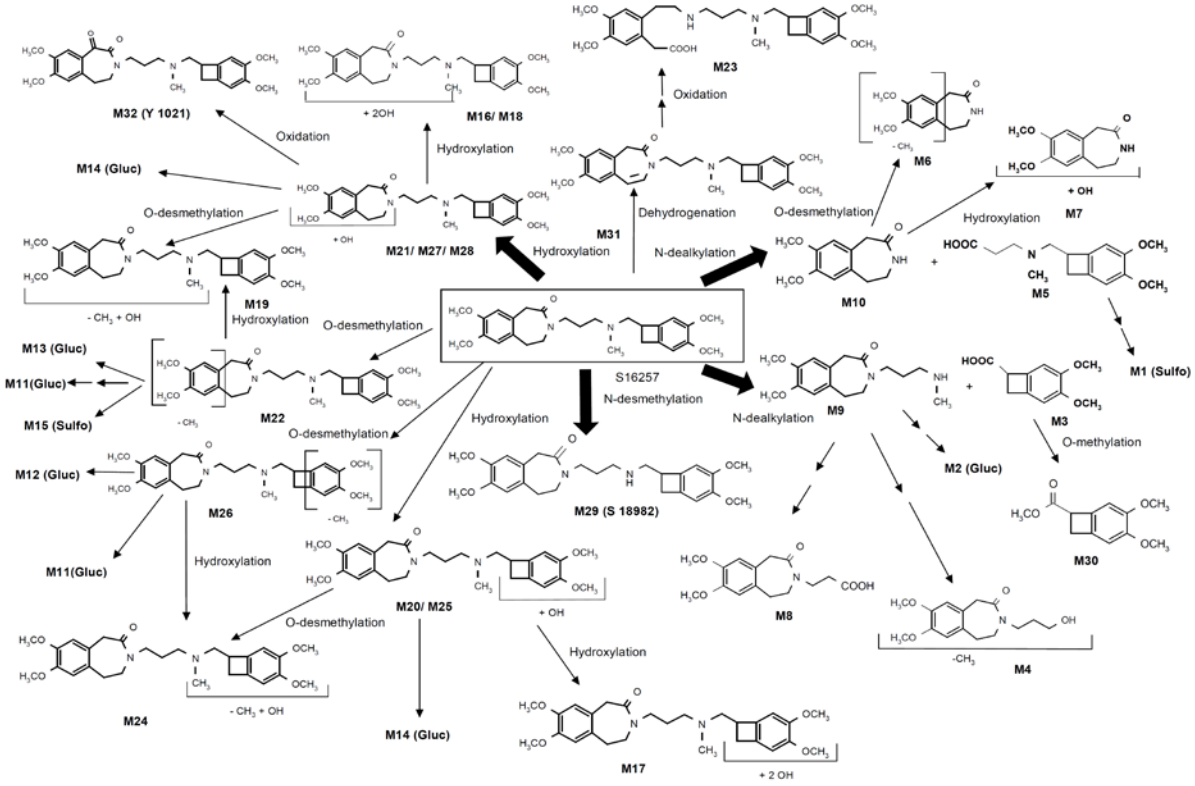
Drug interactions

- Single oral administration of ivabradine at a dose of 5 mg/kg in Wistar rats does not produce an anti-aggregant effect or an interaction with the anti-aggregant effect of acetylsalicylic acid (25 mg/kg, po).
- Oral administration of ivabradine (80 mg/kg/d, po) for 4 days to Wistar rats does not interact with the anticoagulant effect of warfarin
- In unrestrained beagle dogs after oral administration of pharmacologically active doses of diltiazem or digoxin for 7 days, or isosorbide dinitrate for 1 day, there is no pharmacodynamic interaction of a single IV dose of ivabradine (0.5 mg/kg) on BP or ECG conduction parameters. Ivabradine reverses tachycardia induced by verapamil and dinitrates, and limits the PR-interval prolongation induced by verapamil.

4.4.3 Pharmacokinetics

Metabolic pathways

Figure 6. Ivabradine Metabolic Pathways



ADME in Animals

Table 11. Ivabradine ADME in Rat and Dog

General features	Parameter	Rat	Dog
Absorption:	t_{max} (h)*:	~0.3	~1
	Absorption (%):	≥80	≥31
	Bioavailability (%):	40 (M) - 60 (F)	~40
Distribution:	fu (%):	~40	~30
	B/P ratio:	~0.9	~0.8
	Vd (L/kg)*:	~3.4	~1
Metabolism:	Metabolic pathways:	Dealkylation, hydroxylation, dehydrogenation (+ conjugation in rat and dog)	
	S 18982/Ivabradine AUC ratio (%)*:	~1 - 10	~10 – 20
Excretion:	CL (mL/min/kg)*:	66 to 32[a] (M) ~40 (F)	~15
	% of CL:	~5	~5
	$t_{1/2}$ (h)*:	6 to 9[b] (M) 14 (F)	≤2
	Feces (%):	~80	~60
	Urine (%):	~20	~40

B/P ratio: Blood to plasma ratio; Vd: Volume of distribution. *: At steady state
a: For doses of 2.3 to 37 mg/kg/d. b: For doses of 3 to 200 mg/kg/d

Other PK Observations (per sponsor's PK written summary)

- *Dog most similar to human in its PK and metabolism*
- *After oral administration to rat and dog over a large range of doses, ivabradine was rapidly and almost completely absorbed, with a moderate bioavailability of ~40% attributed to the first pass metabolism. Plasma protein binding was moderate at 60 to 70% bound in vitro. The PK was linear over a large range of doses with an overall minimal repeat dose effect in mature rats or dogs. A time-dependent effect was observed in juvenile rats and attributed to development changes in the hepatic expression of drug-metabolizing enzymes. A gender effect was evident in juvenile and mature rats and CD-1 mice; plasma exposure was higher in females than males at equivalent doses.*
- *Ivabradine was highly permeable in vitro and also a substrate of P-gp. Ivabradine and its metabolites rapidly equilibrated in most tissues; however there was no significant uptake into brain or testes likely due to active-efflux from those tissues.*

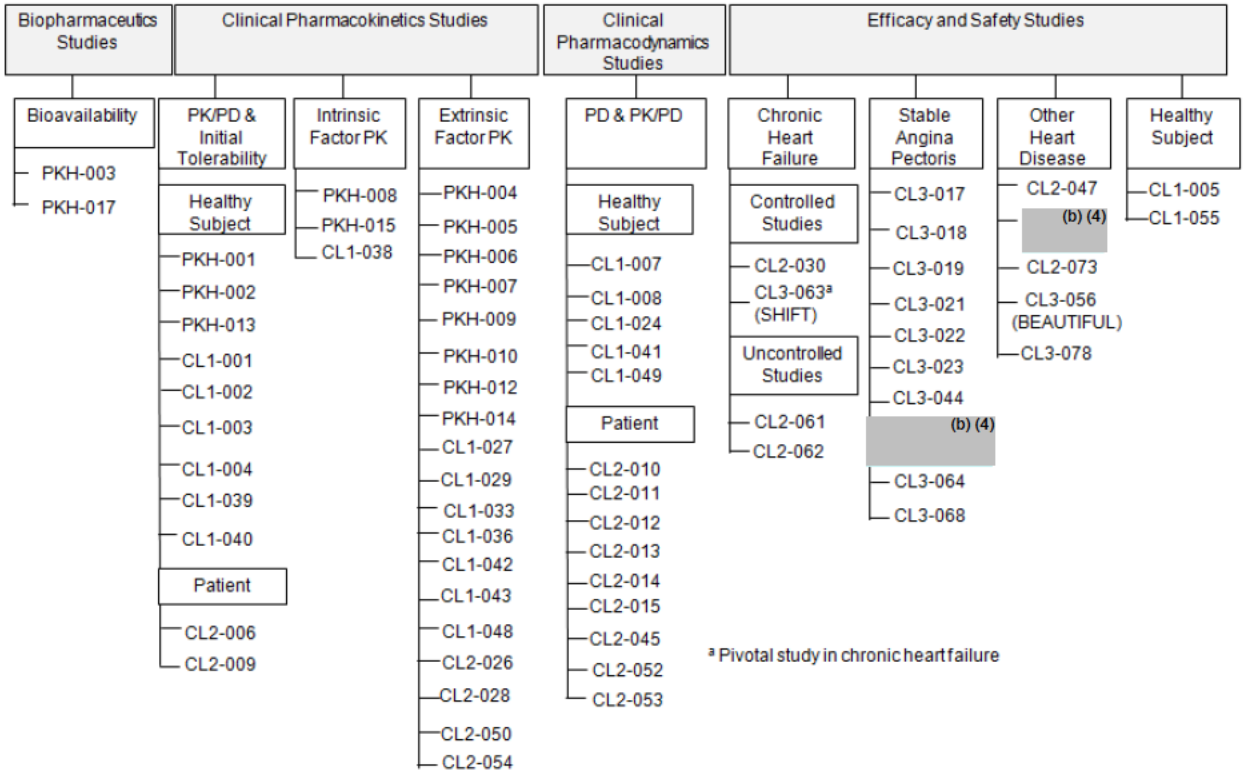
Binding to pigmented structures in the uveal tract was reversible and attributed to binding to melanin.

- *In the rat, ivabradine distributed into amniotic fluid and was excreted in maternal milk.*
- *Ivabradine was extensively metabolized by oxidation. The metabolic profile was similar in preclinical species and human. It was neither an inducer nor an inhibitor of the main drug-metabolizing enzymes and it was not predicted to cause significant drug-drug interactions with CYP3A substrates.* (b) (4) *clinical interactions with OCT2 substrates are possible. In human, metabolism in vitro was mediated by CYP3A4 and subject to inhibition by various CYP3A4 inhibitors, such as cyclosporine A, ketoconazole, and ritonavir. Precaution is advised with the concomitant use of ivabradine strong and moderate CYP3A4 inhibitors or inducers. Ivabradine does not undergo bioconversion to the R-enantiomer.*
- *In rat and dog, the heart-rate reduction (HRR) showed a rapid onset of activity with changes in HR over time that were well related to the plasma levels after oral administration.*

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Figure 7. Completed Ivabradine Clinical Studies



Notes: PK: pharmacokinetics; PD: pharmacodynamics; CL1-: phase 1 study; PKH-: phase 1 study; CL2-: phase 2 study; CL3-: phase 3 study. Adapted from Clinical Overview, p.13

5.2 Review Strategy

In general, Dr. Dunnmon conducted the efficacy review, and Dr. Beasley conducted the safety review. Our reviews focused on the SHIFT-HF trial however we also reviewed the data in BEAUTIFUL, both as a whole and as a subpopulation similar to that studied in the SHIFT trial.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1.1 SHIFT-HF (also known as np29800 or CL3-16257-063)

Effects of ivabradine on cardiovascular events in patients with moderate to severe chronic heart failure and left ventricular systolic dysfunction: a three year randomized, double-blind, placebo-controlled, international, multicenter trial

5.3.1.2 Study Design and Objectives

The primary objective was to demonstrate the superiority of ivabradine over placebo in the reduction of the composite endpoint of CV mortality and hospitalizations for worsening heart failure in patients with moderate to severe chronic heart failure and reduced left ventricular ejection fraction receiving currently recommended HF therapy.

The secondary objectives included overall mortality, death from heart failure, morbidity, functional capacity, and clinical symptoms of heart failure. There were also several ancillary sub studies with endpoints that are discussed in **Section 5.3.1.7**.

Enrollment was planned in 600 centers in 35 countries, all *outside of* the United States

5.3.1.3 Study Duration/Dates

The planned study duration for each participant was from 12 to 36 months.

Table 12. Important dates in SHIFT-HF trial

Final protocol completed	April 18, 2006
Amendment 1 applicable in Poland	September 5, 2006
First visit, first subject	September 26, 2006
Amendment 2 applicable in United Kingdom	March 21, 2007
Amendment 3 applicable in Austria	December 5, 2007
Amendment 4 applicable in India	December 26, 2007
Amendment 5 global (because of BEAUTIFUL)	September 10, 2008
Last patient randomized	June 1, 2009
Amendment 6 global	June 25, 2009
Common study end date for efficacy analysis	March 31, 2010
Last visit, last subject	April 19, 2010
SAP finalized	May 28, 2010
SHIFT database lock	May 31, 2010
SHIFT treatment allocation unblinded	June 1, 2010
Date of SHIFT report	October 21, 2010
NDA data cut-off	October 25, 2013
120 day safety update data cut-off	April 25, 2014

5.3.1.4 Study Sample Size and Power Considerations

This was an event driven study that was scheduled to continue until 1600 (Amendment 5) primary composite endpoints were reached. The number of events required and sample size were chosen in order to detect a true difference between placebo and ivabradine using a two sided log rank test at a 5% type I error rate. 1600 first events were necessary to show a difference between the survival distribution of placebo group and that of ivabradine corresponding to a 15% relative risk reduction with 90% power, based on an

expected mean follow-up duration of 2.25 years and assuming an annual incidence rate of the primary composite endpoint of 14% in the placebo group. The expected incidence of non-cardiovascular death was 1% at 2 years. The expected relative risk reduction with ivabradine was 17%.

It was also estimated that ~47% of the overall population would be treated with at least half of the target dose of beta-blocker at randomization, which is around 3000 patients. Assuming the same risk assumptions as for the overall population, this would result in at least 633 events allowing detection of a relative risk reduction of 20% in favor of ivabradine with 80% power.

There was an interim analysis (per 4/14/2008 protocol) to be performed during the study and it was to be described in the charter of the DMC.

5.3.1.5 Study Population

Key SHIFT Inclusion Criteria

- Adult subjects with stable systolic heart failure New York Heart Association (NYHA) Class II, III, or IV for at least 4 weeks
- Optimal and unchanged CHF medications and doses for at least 4 weeks
- Documented hospital admission for worsening heart failure within 12 months
- Electrocardiographic documentation of normal sinus rhythm with resting heart rate ≥ 70 bpm
- Left ventricular systolic dysfunction with ejection fraction ≤ 35% within the previous 3 months

Key SHIFT Exclusion Criteria

- Previous cardiac transplantation or on list for cardiac transplantation
- Use of intravenous inotropic therapies
- Congenital heart disease
- Severe aortic or mitral stenosis, severe aortic regurgitation, or severe primary mitral regurgitation, or scheduled surgery for valvular heart disease
- Women who were pregnant, breast-feeding
- Recent (less than 2 months prior to selection) MI or coronary revascularization
- Scheduled coronary revascularization
- Stroke or cerebral transient ischemic attack within the previous 4 weeks
- Active myocarditis
- History of symptomatic or sustained (≥ 30 sec) ventricular arrhythmia unless a cardioverter defibrillator was implanted
- Any cardioverter defibrillator shock experienced within the previous 6 months
- Cardiac resynchronization therapy (CRT) started within the previous 6 months
- Pacemaker with atrial or ventricular pacing (except bi-ventricular pacing) > 40% of the time, or with a stimulation threshold at the atrial or ventricular level 60 bpm

- familial history or congenital long QT syndrome or treated with selected QT prolonging products
- Permanent atrial fibrillation or flutter
- Sick sinus syndrome, sinoatrial block, 2nd and 3rd degree atrio-ventricular block
- Severe or uncontrolled hypertension
- Sitting systolic blood pressure < 85 mmHg or current symptomatic hypotension
- Known moderate or severe liver disease (Child-Pugh score > 7), ALAT or ASAT > 3 times the upper limit of normal values
- severe renal disease (serum creatinine > 220 µmol/L (2.49 mg/dL)
- Patients requiring a treatment which is prohibited during the study or for whom such a treatment is considered:
    - Non-dihydropyridine calcium channel blockers, diltiazem and verapamil
    - Vaughan-Williams class I antiarrhythmics
    - Strong cytochrome CYP3A4 inhibitors:
        - Macrolide antibiotics known to be strong CYP3A4 inhibitors (e.g. clarithromycin, erythromycin, telithromycin, josamycin, etc.)
        - Cyclosporine
        - Antiretroviral drugs (e.g. ritonavir, nelfinavir, saquinavir, delavirdine, etc.)
        - Azole antifungal agents administered by systemic route (e.g. ketoconazole, itraconazole, etc.)
        - Nefazodone

Reviewer's comment: The protocol was inconsistent with respect to QT prolonging drugs. They were initially an exclusion criterion, but during the study, initiation of these drugs was "not recommended", but did not necessarily mandate withdrawal. Drugs meeting this description that were identified in the protocol included: amiodarone, bepridil, sotalol, ibutilide, mefloquine, halofantrine, pentamidine, cisapride, sparfloxacine, pimozide, ziprasidone, sertindole, haloperidol, and imipraminic antidepressant drugs. The concern was further prolongation of the QT interval due to ivabradine-induced bradycardia. The sponsor recommended close ECG follow-up of any patient taking these drugs in combination with blinded study drug, and that study drug be dose-reduced or stopped according to the measured QT.

The sponsor also specifically addresses the simultaneous use and/or initiation of treatments that may cause bradycardia following randomization to study drug as follows:

"Amiodarone and beta-blockers are likely to have an additive effect with the HR lowering effect of ivabradine. Patients on study treatment receiving concomitant HR lowering medications and presenting with low HR on the resting standard 12-lead ECG or with signs or symptoms potentially related to bradycardia were to have the study drug dose decreased or withdrawn. If the addition of a beta-blocker to a patient's therapeutic regimen for heart failure was considered appropriate after

randomization, this medication was to be introduced at low doses and increased progressively (as recommended). A 12-lead ECG was to be performed 2 weeks after starting the beta-blocker and 2 weeks after each dose increment, and it was possible that the ivabradine dose (or matching placebo) would have to be decreased or stopped."

Key SHIFT Withdrawal Criteria

- HR < 50 bpm) or symptoms related to bradycardia in patients treated with the lowest dose of the study medication
- Loss of sinus rhythm (e.g. permanent atrial fibrillation)
- pacing more than 40% of the time or with a stimulation threshold at the atrial or ventricular level ≥ 60 bpm
- Occurrence/diagnosis of sick sinus syndrome
- Important sino-atrial block
- Administration of a strong cytochrome P450 3A4 (CYP3A4) inhibitor (could resume ivabradine when CYP3A4 inhibitor stopped for 5 half-lives of the CYP3A4 inhibitor, at the last dose of ivabradine received)

5.3.1.6 Procedures

SHIFT Randomization

Subjects were to be stratified by two factors: center and beta-blocker intake entered in the IVRS at the time of the randomization call by telephone or internet. Subjects were randomized to double-blind placebo or ivabradine.

Reviewer comment: There was a discrepancy in 37 subjects between the information entered in IVRS and what was actually collected, per the following table. The Applicant (and the reviewer) used the information collected and cleaned on the CRF for their beta-blocker analyses.

Table 13. FDA SHIFT Analysis: IVRS versus actual beta-blocker at randomization in SHIFT

	Ivabradine	Placebo	Total
IVRS beta-blocker yes, but actually no beta-blocker at randomization	11	9	20
IVRS beta-blocker no, but actually taking beta-blocker at randomization	7	10	17

Reviewer's analysis: Data\tab\rand\random.sas. dataset random

SHIFT Treatment

The study included a pre-randomization period (from Selection visit ASSE to Inclusion visit D000) which also included a run-in period of no treatment for 14 days.

Subjects were started on ivabradine 5 mg every 12 hours (BID) during meals or placebo on Day 0 (D000) and continued it until Visit D014 (first Titration visit). At Day 14, Day 28 and subsequent visits, the investigator was to adjust the dose per guidelines based on the HR on the resting 12-lead ECG. The ultimate dosing decision, however, was the investigator's. Deviations from these guidelines were to be documented in the eCRF. The study drug was discontinued at the TERM visit. At the end of the study, there was no dose down titration.

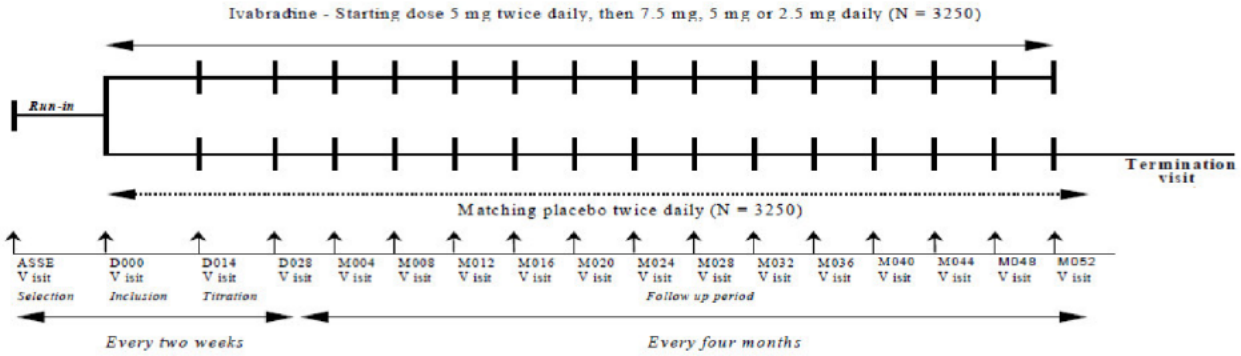
Table 14. Guidelines for treatment titration in SHIFT

Visit Day 14: HR on resting 12-lead ECG	Dose to continue
> 60 bpm	7.5 mg BID or matching placebo
50 – 60 bpm	5 mg BID or matching placebo
< 50 bpm or signs, symptoms likely due to bradycardia	2.5 mg BID or matching placebo
Visit Day 28, subsequent scheduled visits, and unscheduled visits: HR on resting 12-lead ECG	
≥ 50 bpm	Maintain previous dose
≥ 60 bpm & taking 2.5 mg or 5 mg BID	Increase to next upper dose
< 50 bpm or symptoms likely due to bradycardia & taking 5 mg or 7.5 mg BID	Decrease to next lower dose
< 50 bpm or symptoms likely due to bradycardia & taking 2.5 mg	Stop the treatment

Investigational product was given as a single tablet which was packaged in blister strips (30 per strip).

Schedule of Visits
Following Visit D028, patients had visits every four months until the end of the trial, according to the figure below:

Figure 8. SHIFT Study Plan



Patients were scheduled to have their last visit/contact between the 1st of February 2010 and the 31st of March 2010.

Adapted from SHIFT final SAP page 5/134.

SHIFT Schedule of Investigations

Figure 9. SHIFT Schedule of Investigations

VISITS / Procedures	Selection ASSE	Inclusion D000	Treatment period														
			D 014	D 028	M 004	M 008	M 012	M 016	M 020	M 024	M 028	M 032	M 036	M 040	M 044	M 048	M 052	TERM
Informed consent	X																	
Selection / inclusion criteria	X	X																
Relevant medical history	X																	
Prior CHF treatments	X																	
Concomitant treatments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ejection fraction		X*																
Compliance			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact with (b) (4)		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Allocation of treatments		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Efficacy measurements																		
Pre Specified Event	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Heart rate (12-lead ECG)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NYHA classification	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient global assessment					X		X			X								X
Investigator global assessment					X		X			X			X			X		X
Safety measurements																		
12-lead ECG	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood pressure (SBP, DBP)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory examinations **	X*				X		X			X			X			X		X

* Results to be available before randomisation.

** Blood Clinical Laboratory Tests: haemoglobin, haematocrit, red blood cell count, white blood cell count, platelet count, sodium, potassium, creatinine, ALT, AST, fasting plasma glucose, total and LDL cholesterol (only at D000 and TERM visits).

Adapted from SHIFT final SAP page 5/134.

SHIFT Premature Withdrawals

When the investigator had no news of a patient, he/she made every effort to make contact (unless the patient had clearly expressed a wish not to be contacted), to obtain the date when the study treatment was discontinued, to establish the reason for the discontinuation, to ask the patient to resume the study procedures or to come to at least one last visit and to suggest that the patient provide the contact details of the physician who could assure follow-up (unless the patient had clearly expressed a wish not to be contacted anymore: i.e. consent withdrawal). The key study data (occurrences and dates of occurrences of the PSEs) could then be obtained from this physician. In case of consent withdrawal, no data were collected after the withdrawal; the data obtained prior to consent withdrawal remained in the database. If all these attempts to contact the patient failed, and if the key study data could not be obtained before the end-of-study visit, the patient was to be declared as lost to follow-up.

5.3.1.7 Efficacy Endpoints

The primary composite endpoint was the time to first occurrence of cardiovascular death or hospitalization for worsening heart failure.

The secondary endpoints included (i) time to occurrence of any of the following non-composite endpoints:

- all cause death,
- death from heart failure,
- cardiovascular death,
- all cause hospitalization,
- any cardiovascular hospitalization, or
- hospitalization for worsening heart failure,

(ii) time to occurrence of the first event of the following composite endpoint: cardiovascular death, hospitalization for worsening heart failure, or hospitalization for non-fatal myocardial infarction (MI), and (iii) change in functional capacity (NYHA class) and clinical symptoms of heart failure (patient and physician global assessment scores, PGA).

Other endpoints included left ventricular remodeling (by ECHO), NT-proBNP, and heart rate variability (by 24-h Holter), quality of life and other patient reported outcomes. Plasma concentrations were also collected for pharmacokinetics.

5.3.1.8 Safety Endpoints

Safety evaluation included regular evaluation of adverse events, vital signs, 12-lead ECG with heart rate, laboratory tests, and 24-h Holter ECG. **See also 7.2.4**.

5.3.1.9 Study Committees

The study included an Executive Committee (EC), Steering Committee (SC), Data Monitoring Committee (DMC) and Endpoint Validation Committee (EVC).
The DMC supervised the safety of the trial and made recommendations concerning the conduct of the study.

5.3.1.10 Identification of Potential Endpoint Events

Investigator Triggers (per the SHIFT protocol)

The Pre-specified Events (PSE) for efficacy were identified by the investigator participating in the study and recorded on the electronic-Case Report Form (e-CRF) AE/PSE page. An e-mail alert was then automatically sent to the monitoring structure, the PSE CRO and I.R.I.S., to inform them that a PSE had occurred. Per the applicant's Adjudication Document (21 May 2014),

> *For all subjects who died from any cause or were hospitalized for any cause, investigators were to report the PSE in the electronic case report form (e-CRF) immediately after being informed of the event. The investigators were required to prepare a PSE file gathering all relevant documentation as specified in the Endpoint Validation Committee (EVC) Charter in Study CL3-063 (Report np29800 Appendix 16.1.10.1.2). This documentation was verified, collected, and redacted of baseline heart rate and identifying information, by the site monitor within 10 days of notification of the PSE. A central medical reviewer also verified the documentation to confirm accuracy and completeness of the PSE file. The PSE file was scanned and placed in an endpoint data management structure operated by a contract research organization (CRO; (b) (4) and made available electronically to an external independent EVC for adjudication. The EVC was blinded to subject identity and to the allocated study treatments as well as to baseline heart rate.*

The following non-automated procedures were incorporated to help assure that no PSEs were missed:

- Adjudication of all deaths and all hospitalizations
- Routine site monitor review of AE source documentation for potential missed events
- Routine site and central medical review of AEs for potential missed events
- EVC review of PSE files, including source documentation, for potential missed events; EVC could independently trigger new PSEs
- PSEs were re-adjudicated if additional documentation was sent by the investigator.

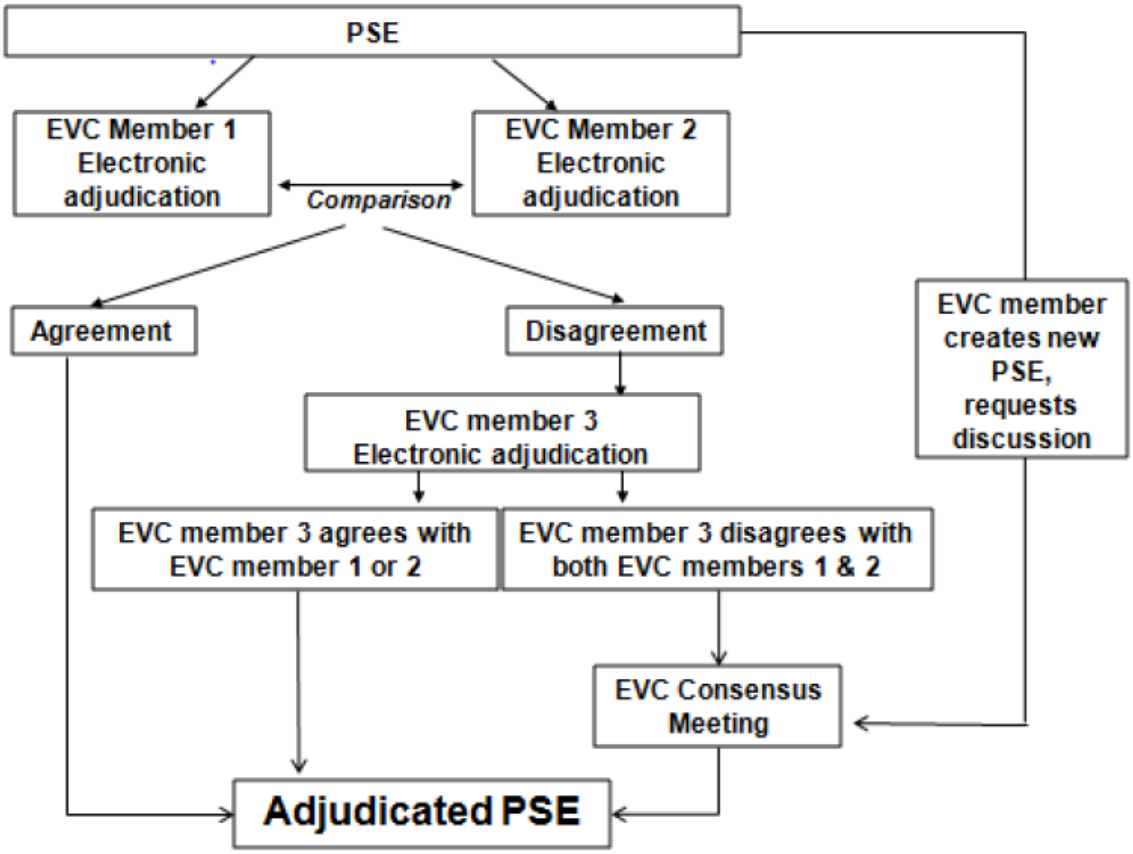
Automated Triggers

- Automated triggering of email alerts for PSEs in e-CRFs
- Automated consistency checks in e-CRFs for any adverse events (AE) with fatal outcome

5.3.1.11 Adjudication Process

Potential PSE events from SHIFT were sent to the Event Validation Committee (EVC) and were to be adjudicated within 10 days of the notification of the event per the process outline in the figure below:

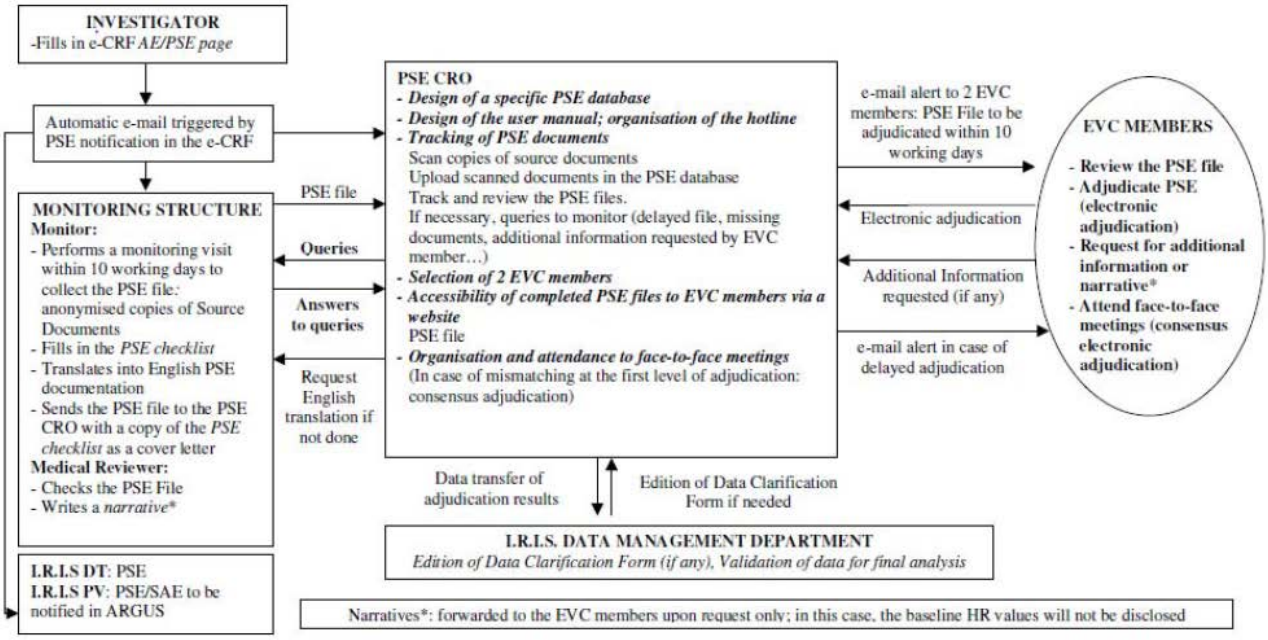
Figure 10. SHIFT Adjudication Process



Adapted from SHIFT EVC Charter 20/31

The communication flows between the EVC members and the other structures of the SHIFT study is shown in the following diagram:

Figure 11. Information Communication Within SHIFT



Adapted from the SHIFT EVC CHARTER 10/31

5.3.1.12 Adjudicated endpoints

The EVC Charter definitions of the study endpoints are found in the Appendix, **Section 9.5**. The endpoints included (as numbered in the appendix):

1. Hospitalization
   - 1.1. Cardiovascular hospitalization
     - 1.1.1. Hospitalization for worsening HF
     - 1.1.2. Hospitalization for MI
     - 1.1.3. Hospitalization for other cardiovascular
     - 1.1.4. Hospitalization for non-cardiovascular
     - 1.1.5. Hospitalization for undetermined cause
2. Deaths
   - 2.1. Cause of Death
     - 2.1.1. All cause death
     - 2.1.2. Cardiovascular death
       - 2.1.2.1. Death from heart failure
       - 2.1.2.2. Death from MI
       - 2.1.2.3. Arrhythmic death or presumed arrhythmic death (SCD)
       - 2.1.2.4. Death from other cardiovascular causes
     - 2.1.3. Non cardiovascular death
     - 2.1.4. Death of unknown cause
   - 2.2. Mode of death

2.2.1. Sudden
2.2.2. Non sudden

3. Relationship between clinical events and PSE classification

5.3.1.13 Statistical Analysis Plan

The only SAP submitted was the final SAP dated May 28, 2010 (after the common study end date of March 31, 2010).

The superiority of ivabradine compared to placebo was tested on the applicant's randomized set (n=6505) during the entire follow-up period. A cox proportional hazard model with adjustment for the stratification factor of previous beta-blocker intake was based on information entered into the IVRS. The same analysis was used on each component of the composite primary endpoint and on the secondary endpoints. It was also planned to do the same analyses on subjects receiving at least half the target daily beta-blocker dose at randomization (RS-BB-DOSE). An interim analysis was planned.

> *Reviewer's comment: SHIFT randomized 6558 subjects. The applicant excluded 7 subjects (2 ivabradine) that did not meet inclusion criteria and were never treated, and 46 subjects from two Polish sites for study misconduct. The decision to exclude the sites was made prior to database lock and unblinding. It is unclear when the decision was made to exclude the 7 subjects that did not meet inclusion criteria.*

Subjects were to have their last visit/contact between February 1, 2010 and March 31, 2010. All efficacy analyses on the primary composite endpoint, CV deaths and hospitalization for WHF were to include all events that occurred before or at the patient termination visit and before March 31, 2010.

Please refer to the Biometrics review for more information on the interim analyses and SAP.

5.3.1.14 Protocol Amendments

Table 15. Protocol Amendments, SHIFT

	Important Changes
Final protocol completed	April 18, 2006
Amendment 1 applicable in Poland	September 5, 2006 Women of childbearing potential should have a negative urinary pregnancy test before inclusion.
First visit, first subject	September 26, 2006
Amendment 2 applicable in United Kingdom	March 21, 2007 Women of childbearing potential should have a negative urinary pregnancy test before inclusion. The method of LVEF assessment for inclusion into the study was to be either by echocardiography or magnetic resonance imaging.
Amendment 3 applicable in Austria	December 5, 2007 Added Austria as country for recruitment. Women of childbearing potential should have a negative urinary pregnancy test before inclusion. Test was to be repeated every 4 weeks.
Amendment 4 applicable in India	December 26, 2007 Added India as country for recruitment
Amendment 5 global	September 10, 2008 BEAUTIFUL results suggested ivabradine had a smaller effect on heart failure endpoints than predicted. Thus this amendment increased the sample size from 5500 to 7000 patients total and continued the trial until at least 1600 composite endpoints were reached. This was estimated to increase the power of the study to detect a 15% reduction in risk (compared to 17%). A specific evaluation of the efficacy of ivabradine in the population of patients who were receiving at least half the target dose of beta-blockers at randomization was also added. The duration of the study was extended from 36 months to 41 months.
Amendment 6 global	June 25, 2009 Because of lower recruitment rate than expected, the total duration of the trial for the first recruited subjects was extended beyond 36 months (up to 52 months) so that the mean follow-up time was increased. Because of the increase in trial duration, the actual number of primary endpoint reported was higher than expected (1045 at the cutoff date of March 11, 2009). It was estimated that 1600 primary endpoints would

	be reached within one year. Thus, recruitment was stopped early in June 2009 after 6500 patients were randomized. At M036 and M048 visits, investigators were required to perform the Physician Global Assessment and take fasting blood samples from all patients to analyze serum creatinine, hemoglobin, AST, ALT, sodium, and potassium.

5.3.2 BEAUTIFUL (also known as np27426 or CL3-16257-056)

Effects of ivabradine on cardiovascular events in patients with stable coronary artery disease and left ventricular systolic dysfunction. A three-year randomized double-blind placebo-controlled international multicenter study – The BEAUTIFUL study.

5.3.2.1 Study Design and Objectives

This was a randomized, double blind, placebo-controlled, multi-center, international morbidity-mortality study, with two parallel and balanced treatment arms.

The primary objective was to demonstrate the superiority of ivabradine over placebo in the reduction of incidence of the composite endpoint: cardiovascular (CV) mortality, hospital admissions for acute myocardial infarction (MI), hospital admissions for new onset or worsening heart failure (HF) in patients with CAD and LV systolic dysfunction.

The secondary objectives were to assess the effect of ivabradine:

- On hospital admissions for acute coronary syndrome (ACS; MI or unstable angina).
- On hospital admissions for ACS, new onset or worsening HF, coronary revascularizations (composite endpoint).
- On each endpoint of the previously mentioned composite endpoints.
- On mortality related to coronary artery disease (CAD), all-cause mortality.

The tertiary objectives were to assess the effect of ivabradine:

- On the development of diabetes and metabolic syndrome.
- On the evolution of left ventricular ejection fraction (LVEF), fractional shortening and end-diastolic dimension (investigator assessment).
- On the evolution of NYHA classification.

5.3.2.2 Study Duration/Dates

Table 16. Important Dates in BEAUTIFUL Trial

Final protocol completed	24 September 2004

First visit, first subject	20 December 2004
Amendment 1 global	9 February 2005
Amendment 2 applicable in United Kingdom	16 March 2005
Amendment 3 applicable to Holter substudy center	03 January 2006
Amendment 4 applicable to echo/NT-proBNP substudy centers	03 January 2006
Amendment 5 global	11 July 2006
Amendment 6 global	22 January 2007
Defined completion date	15 January 2008
Last visit, last subject	28 February 2008
BEAUTIFUL database lock (b) (4)	25 April 2008
BEAUTIFUL database lock (b) (4)	28 April 2008
SAP finalized	29 April 2008
BEAUTIFUL treatment allocation unblinded (sponsor)	30 April 2008
Date of BEAUTIFUL final study report	9 March 2009

Reviewer's comment: Database for BEAUTIFUL was locked at the CRO 4 days before the SAP was finalized, and the day before unblinding.

5.3.2.3 Study Sample Size and Power Considerations

The planned enrollment was 9650 patients. The Randomized Set was 10,917 patients (5479 to ivabradine, 5438 to placebo).

For a 90% power, 950 events and 9,650 patients were necessary to show a difference between the survival distribution of placebo group and that of ivabradine group, corresponding to a 19% relative risk reduction, with an incidence of the primary composite endpoint of 11% at 2.25 years in placebo group (expected incidence based on previous studies: EUROPA study investigators 2003; (b) (4) (b) (4) and an incidence of non-cardiovascular death of 1% at 2.25 years in both groups.

Due to a higher rate of hospitalisations for new onset or worsening heart failure than anticipated, the 950 expected events were reached when the last included patients were treated for 3 months (instead of the initially planned duration of 18 months), with an approximate overall follow-up of 1.25 years.

5.3.2.4 Study Population

Key BEAUTIFUL Inclusion Criteria

- Male or female

- Aged ≥ 55 years (with no history of diabetes) or ≥ 18 years (with a history of type I or II diabetes)
- Evidence of CAD documented by any of the following:
    - Previous MI (at least 6 months prior to selection)
    - Previous percutaneous or surgical coronary revascularization (at least 6 months before selection)
    - Angiographic evidence of at least 50% narrowing of one or more major coronary vessels
- Must have all of the following
    - Documented sinus rhythm and HR ≥ 60 bpm (changed from ≥ 55 bpm by Amendment No. 1) on a recent (within 24 hours) resting standard 12-lead ECG, AND
    - Left ventricular ejection fraction ≤ 39% on a recently performed measurement (in the previous 4 weeks) from a two-dimensional echocardiography, AND
    - Left ventricular dilatation on an echocardiographically measured short-axis internal dimension at end diastole greater than 56 mm (exam performed in the previous 4 weeks)
- Stable condition (for at least 3 months) with regards to angina and/or heart failure symptoms and on appropriate and stable doses (for at least 1 month) of conventional cardiovascular medications

Key BEAUTIFUL Exclusion Criteria

- A transplanted heart
- Implanted pacemaker or implantable cardioverter defibrillator
- Sick sinus syndrome, sinoatrial block, congenital long QT, complete atrio-ventricular blockade

Key BEAUTIFUL Withdrawal Criteria

Study drug no longer appropriate:

- Prolonged loss of sinus rhythm
- Prolonged (more than 6 months) and permanent pacing induced by a pacemaker implanted to treat an atrio-ventricular block or by a defibrillator (the study treatment was considered as appropriate in the case of prolonged and permanent pacing by a device implanted for cardiac resynchronization therapy) (condition modified by Amendment No. 5)
- Sick sinus syndrome
- Sinoatrial block
- Concomitant administration of a strong cytochrome 3A4 inhibitor

5.3.2.5 Procedures

BEAUTIFUL Randomization

Randomization was stratified by beta-blocker intake at randomization and center.

BEAUTIFUL Treatments

A resting standard 12-lead ECG was performed at each visit for measurement of HR. Decisions about enrollment and dose titrations were based in the HR from that resting ECG as follows:

Figure 12. Guidelines for Treatment Initiation and Titration in BEAUTIFUL

Randomization HR ≥ 60, resting ECG	5 mg BID
Visit Day 15 HR on resting ECG	Dose to continue
≥ 60 bpm	7.5 mg BID or matching placebo
50 – 59 bpm	5 mg BID or matching placebo
< 50 bpm or signs, symptoms likely due to bradycardia	Treatment Discontinued

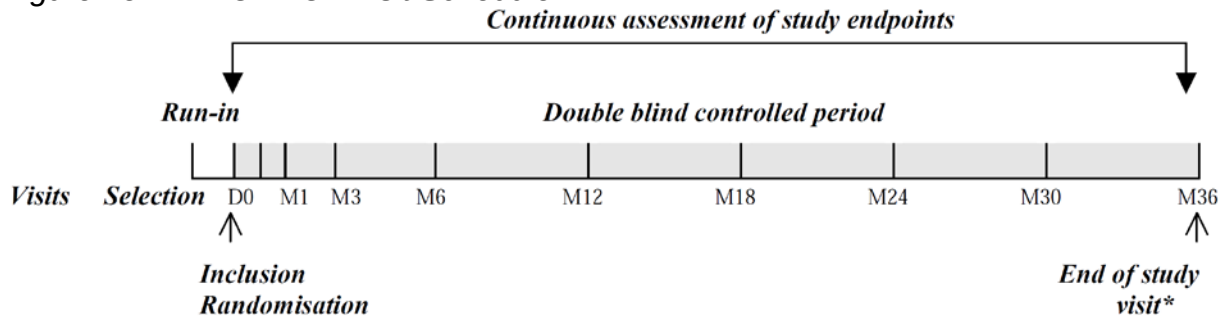
At the M1 and all subsequent visits, the following rules governed dose titrations:

- *Patient receiving 7.5 mg dose and HR ≥ 50 bpm: dose maintained.*
- *Patient receiving 7.5 mg dose and HR < 50 bpm (or patient experiencing signs or symptoms related to bradycardia): dose reduced to 5 mg.*
- *Patient receiving 5 mg dose and HR ≥ 50 bpm and in the absence of signs or symptoms likely to be due to bradycardia: dose maintained.*
- *Patient receiving 5 mg dose and HR < 50 bpm (or patient experiencing signs or symptoms related to bradycardia): study drug discontinued.*

Note that the heart rate entry criteria for inclusion, as well as subsequent heart rate limits used for dose titrations were increased by Amendment-1 (by 5bpm) to the values indicated above. Up-titrations after the D15 visit were not allowed.

BEAUTIFUL Visit Schedule

Figure 13. BEAUTIFUL Visit Schedule



Adapted from BEAUTIFUL FSR 63/7664

BEAUTIFUL Schedule of Investigations

Figure 14. BEAUTIFUL Schedule of Investigations

	Run in		Double-Blind Treatment Period								
	Sel	D0	D15	M1	M3	M6	M12	M18	M24	M30	M36[1]
Informed consent/demography	X										
Selection/Inclusion Criteria	X	X									
Clinical examinations											
Resting Standard 12-lead ECG/HR	X	X	X	X	X	X	X	X	X	X	X
Height: x / Waist Circumference X		x/X					X		X		X
Weight		X	X	X	X	X	X	X	X	X	X
NYHA class		X									X
Sitting Blood Pressure	X	X	X	X	X	X	X	X	X	X	X
Cardiac Echocardiogram		X[2]									X
Blood Samples for Lab Tests[3]		A[2]	B	B	B	B	A	B	A	B	A
Adverse Events (+PSEs)		X	X	X	X	X	X	X	X	X	X
Compliance assessment			X	X	X	X	X	X	X	X	X
Substudies											
24-hour Holter ECG recording[4]		X		X		X					
Echocardiographic central assessment[5]		X			X		X				
NT-proBNP blood sample[5]		X			X		X				

1: The M36 visit was possible only for patients recruited early into the study. The end-of-study-visit for all other patients (irrespective of their follow-up duration) comprised the M36 assessments.
2: Results locally read, to be available before randomisation.
3: Blood Clinical Laboratory Tests:
Type "A": haemoglobin, haematocrit, red blood cell count, white blood cell count, platelet count, sodium, potassium, creatinine, ALAT, ASAT, fasting plasma glucose, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol (calculated from the Friedewald formula).
Type "B": sodium, potassium, creatinine, ALAT and ASAT.
4: Planned in 700 patients, added by amendment 3.
5: Planned in 660 patients, added by amendment 4.
UNSCHEDULED VISITS could include: clinical examination, blood pressure measurement, resting standard 12-lead ECG, HR measurement, type "B" clinical laboratory tests, and safety assessment.

Adapted from BEAUTIFUL FSR 63/7664

BEAUTIFUL Premature Withdrawal

Patients for whom the study drug was discontinued could remain in the study if they continued to attend the scheduled visits, or if they (or their general practitioner) were contactable (by telephone or other). When the investigator had no news of a patient, he/she made every effort to make contact (unless the patient had clearly expressed a wish not to be contacted), to obtain the date when the study treatment was discontinued, to establish the reason for the discontinuation, to ask the patient to resume the study procedures or to come to at least one last visit and to suggest that the patient provide the contact details of the physician who would assure follow-up. The key study data (occurrences and dates of occurrences of the PSEs) could then be obtained from this physician. If all these attempts to contact the patient failed, all actions implemented were documented in the medical file and if the vital status could not be obtained before the 15 January 2008, the patient would be declared as lost to follow-up. (BEAUTIFUL FSR 57/7664)

5.3.2.6 Efficacy Endpoints

The following were the prespecified efficacy and safety endpoints in the original BEAUTIFUL protocol:

- Primary efficacy endpoint: Time to occurrence of the first event of one of the following: cardiovascular mortality, hospital admission for acute myocardial infarction, hospital admission for new onset or worsening heart failure.

- Secondary efficacy endpoints:
  - Composite endpoint. Time to occurrence of the first event of one of the following: hospital admission for acute coronary syndrome (acute myocardial infarction or unstable angina), hospital admission for new onset or worsening heart failure, coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft).
  - Non-composite endpoints. Time to occurrence of each endpoint of the previously mentioned composite endpoints, time to occurrence of mortality related to coronary artery disease, total mortality, fatal and non-fatal acute myocardial infarction.

- Tertiary efficacy endpoints
  - Development of diabetes, development of metabolic syndrome, evolution of echocardiographic left ventricular ejection fraction, fractional shortening and end-diastolic dimension.

5.3.2.7 Safety Endpoints

No specific safety endpoint was identified in the original BEAUTIFUL protocol. What was planned was a general safety appraisal throughout the study by the Data and Safety Monitoring Board. *At the end of the study, a detailed safety appraisal will be conducted on adverse events, on the evolution of blood pressure and heart rate, and on abnormalities observed from the electrocardiographic recordings.*

5.3.2.8 Study Committees

Data Monitoring Committee

A summary of adjudicated endpoints was to be transmitted regularly to the statistician of the Data and Safety Monitoring Board (DSMB) who had access to the code list of treatments. The DSMB was to be charged with supervising the safety aspects of the study. The unblinded documentation was to remain confidential and not made available to anyone outside the DSMB. The DSMB was changed to DMC by amendment 5.

Event Validation Committee

The pre-specified events that were reviewed by the Endpoint Validation Committee are: deaths of any cause, acute MI, hospital admissions for unstable angina, hospital admissions for new onset or worsening heart failure, coronary revascularizations (PCI or CABG). Some of the pertinent definitions of PSE, as defined in the EVC charter, were as follows (per the original protocol):

- Cardiovascular death will be defined as (i) a CAD death meeting the definition below (ii) death related to a vascular investigation/procedure/operation (procedure related death) and (iii) other cardiovascular death – for example, a stroke, ruptured aneurysm, or pulmonary embolism.
- CAD death will include death due to heart failure, death due to MI, death due to a cardiac investigation/procedure/operation (procedure related death).
- Acute MI: All definite MI will be counted as events, whether they occurred spontaneously or as the direct consequence of an investigational procedure or operation. A diagnosis of acute MI will be made if a typical rise of biochemical markers of myocardial necrosis [troponin, creatine kinase (CK), MB fraction of CK (CK-MB) or, when exceptionally unavailable, alanine amino-transferase (ALT), aspartate amino-transferase (AST) or myoglobin] are observed with at least one of the following: (a) ischemic symptoms i.e. cardiac ischemic type pain lasting at least 20 minutes or pulmonary edema or cardiogenic shock not otherwise explained (b) development of pathologic Q waves on the ECG (0.04 second in duration) in at least two consecutive ECG leads not present on an ECG recorded before the current event (c) ECG changes indicative of ischemia (transient ST segment

elevation or depression or new left bundle branch block) (d) coronary artery intervention (e.g. coronary angioplasty).

5.3.2.9 Identification of Potential Endpoint Events

Investigator Triggers (per the BEAUTIFUL protocol)

Per the sponsor's BEAUTIFUL Adjudication Document (19 May 2014) regarding the identification of PSEs, "*For all subjects who died from any cause or were hospitalized for acute myocardial infarction (MI), unstable angina, new onset or worsening heart failure, or coronary revascularization, investigators reported the event in the paper case report form (CRF) within 24 hours of awareness and were requested to prepare a PSE file gathering all relevant documentation as specified in the Endpoint Validation Committee (EVC) Charter."*

Non-automated procedures that were incorporated to help assure that no PCE was missed include:

- Adjudication of all deaths for acute MI, unstable angina, new onset or worsening heart failure, and coronary revascularization
- Comparisons and checks between PSEs reported in the CRF via clinical database and PSEs adjudicated via adjudication database
- Routine site monitor review of adverse event (AE) source documentation for potential missed events
- Routine local and central medical review of AEs for potential missed events
- EVC review of PSE files, including source documentation, for potential missed events; EVC could independently trigger new PSEs
- PSEs were re-adjudicated if additional documentation was sent by the investigator.

Automated Triggers

None identified.

5.3.2.10 Adjudication Process

Potential PSE events from BEAUTIFUL were sent to the Event Validation Committee (EVC) and adjudicated per the following instructions to the EVC committee members (from the BEAUTIFUL EVC Charter, 9-11/26):

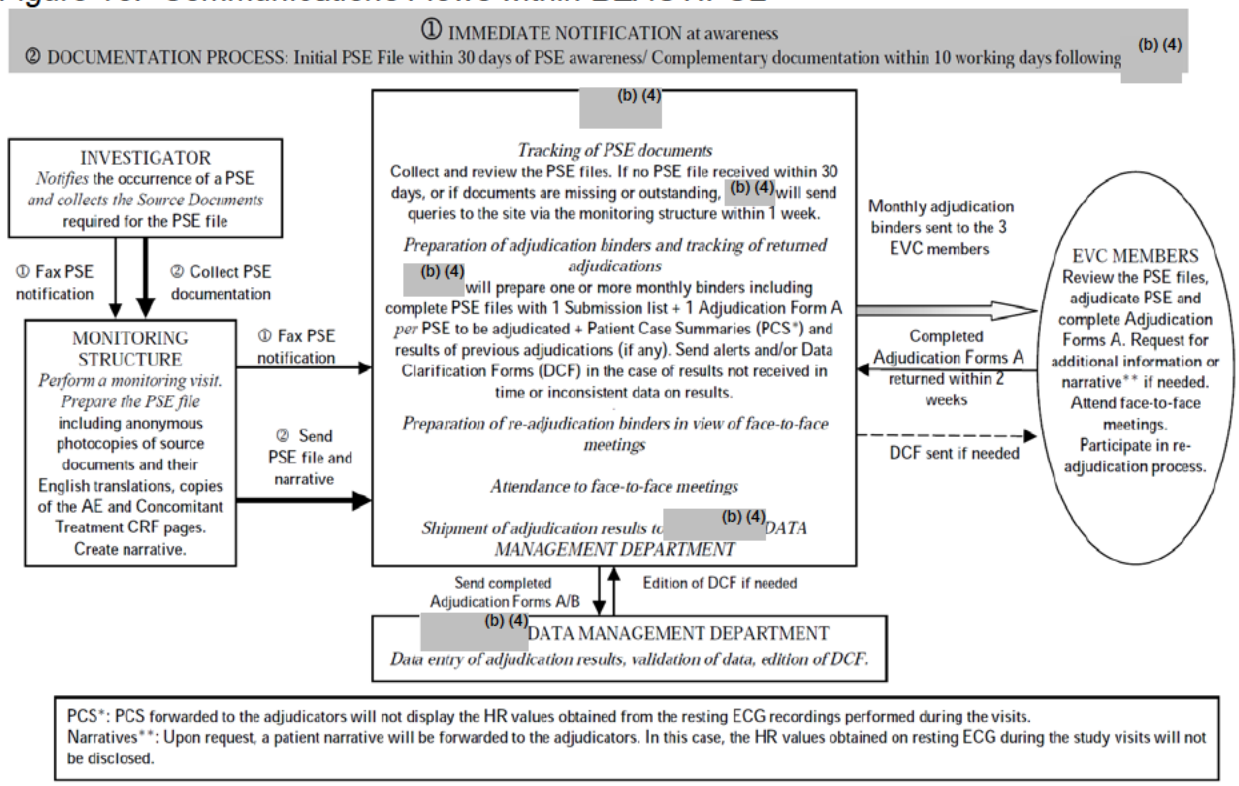
> *The EVC members will review independently and in parallel the documentation supporting the events reported as PSE by the investigators and will be responsible for the impartial adjudication (confirmation, modification or invalidation of the diagnosis). The definitions to be used by the EVC members for their adjudications*

are presented in Appendix 1. In order to obtain an unbiased review of the PSE files, they will be blinded to the treatment assigned to the patients and HR values recorded by the investigators during the study visits on resting ECG.
In the case of discrepancy in the adjudication between at least 2 of the 3 experts of the EVC, the event will be reviewed and jointly adjudicated by the 3 EVC members during a face-to-face meeting.

In the case of mismatching adjudication or additional information obtained for a PSE previously submitted for adjudication, the PSE documentation (PSE file) will be reviewed during a face-to-face meeting and the case will be jointly re-adjudicated by the 3 EVC members. These meetings will be attended by the 3 adjudicators of the EVC, at least one (b) (4) representative, and at least one (b) (4) representative.

The communication flows between the EVC members and the other structures of the BEAUTIFUL study as shown in the following diagram:

Figure 15. Communications Flows within BEAUTIFUL



Adapted from BEAUTIFUL EVC Charter 8/26

5.3.2.11 Statistical Analysis Plan

The sponsor reports that: the statistical analysis was performed by the (b) (4) according to the statistical analysis plan based on the protocol and amendments and finalized on 29 April 2008, before study unblinding.

The randomization was centralized through an IVRS, balanced between the two treatment groups, and stratified by center (781 centers) and BB intake (yes/no).

The primary efficacy analysis was for the superiority of ivabradine over placebo in the reduction of cardiovascular mortality, hospital admissions for acute myocardial infarction or hospital admissions for new onset or worsening heart failure. The treatment effect was evaluated using an intention-to-treat analysis on this primary composite endpoint and tested with a log rank test stratified on beta-blocker intake at randomization with a significance level of 5% (two-sided). Sensitivity analysis was performed with adjustment for BB intake.

The Data Monitoring Committee performed two interim analyses for which the type I error rate was fixed at 0.1% using the Peto group sequential procedure. This choice had no significant impact on the type I error rate used for the final analysis that remained at 5%.

An alpha conserving strategy for evaluation of secondary endpoints was not pre-specified.

Key changes to the SAP were incorporated according to the sponsor prior to study unblinding included:

- Particular interest was given to randomized patients with baseline heart rate above 70 bpm (median value observed in this study). All endpoints analyses planned on the randomized set were performed on this subgroup of patients, which comprised as many endpoints as were required to power the entire study as originally planned.
- Additional subgroups of interest were studied, including patients with: previously documented myocardial infarction, previous revascularization, history of hypertension, NYHA (class I or II / class III) at baseline, LVEF (< 35 / ≥ 35%) at baseline.
- For logistical reasons, the window for the end-of-study visits (which was to be 15 September 2007 - 15 January 2008) was widened to 30 August 2007 – 15 September 2008.
- Additional secondary endpoints of interest were studied:
    - First event among cardiovascular death and hospitalisation for new onset or worsening heart failure
    - First event among cardiovascular death and hospitalisation for acute MI
    - First event among ACS and coronary revascularization
- The evolution of HR was studied in terms of efficacy instead of safety.

- A theoretical termination period was defined during the study with the Executive Committee: patients were scheduled to have their last contact between the 30th of August 2007 and the 15th of January 2008. The censorship process planned in the protocol was completed accordingly.
- Many prognostic factors are found in published reports as well as in exploratory investigations on blinded data of the current study. A Cox model including all these factors was not considered to ensure greater precision and therefore, the robustness of the main results was studied using estimate of the treatment effect in subgroups of interest, defined from prognostic factors.
- Endpoints analyses were focused on intent to treat approach.
- Changes under treatment and 95%CI for changes in echocardiographic parameters were no longer to be provided. A brief description of investigator's evaluation was given as a specific substudy with centralized reading was set up (Amendment No. 4) in order to investigate this topic more precisely.
- Safety analyses were focused on emergent adverse events.
- EAE that occurred on treatment were also investigated in order to detect any potential safety issues with the study drug.
- Particular attention was paid to deaths and hospitalisations for any cause as reported by the investigators.

Key changes to the SAP were incorporated according to the sponsor after study unblinding included:

- Complementary (unplanned) analyses:
    - Background beta-blocker use: mean daily dose and use of target (and ½ target) dose
    - Respect of dose titration according to HR criteria (up-titration with HR ≥ 60 and non-titration with HR < 60)
    - Demography, risk factors, documentation of disease, baseline heart rate were described for the following pre-defined subgroups and other subgroups of interest:
        - NYHA class I or II / class III.
        - NYHA class I / class II.
        - LVEF ≥ 35% / < 35%.
        - Diabetes with / without.
        - Metabolic syndrome with / without.
        - Previous MI with / without.
        - Previous revascularization with / without.
        - History of hypertension with / without.
        - Age ≥ 75 years / < 75 years.
        - Anginal pain as limiting factor for physical activity in patients scored NYHA II or III / no anginal pain (NYHA I or II or III).

- Additional descriptions of blood pressure, specific concomitant treatments taken at randomization, follow-up and study drug intake were provided for the following subgroups:
  - Patients with baseline HR < 70 bpm
  - Beta-blocker intake at randomization: with / without.
  - Men / Women
  - Age ≥ 75 years / < 75 years
  - Anginal pain as limiting factor for physical activity in patients scored NYHA II or III / no anginal pain (NYHA I or II or III)
  - NYHA class I / class II / class III.
- Update of code list for concomitant treatments using digitalis
- Additional analyses in the pre-defined RS-HR70: evolution of HR, evolution of tertiary outcomes
- Analyses in patients with HR < 70 bpm: additional secondary endpoints (secondary composite endpoints, characteristics of deaths (cause and mode), evolution of HR)
- Analyses in patients receiving or not background beta-blockers at baseline (RS and RS-HR70): individual secondary endpoints, characteristics of deaths (cause and mode), and evolution of tertiary outcomes
- Analyses in men and women, and in patients with LVEF ≥ or < 35%: characteristics of deaths (cause and mode)
- Analyses in the subgroups of patients with anginal pain at baseline / without anginal pain: primary endpoint, components, individual and secondary composite endpoints, characteristics of deaths (cause and mode)
- Analyses in the subgroup of patients with NYHA class I or class II or class III: primary endpoint and components, all-cause mortality, characteristics of deaths (cause and mode)
- Analyses of emergent visual symptoms (phosphenes, blurred vision, visual disturbance) on treatment in Safety Set
- Analyses of emergent AEs and visual symptoms on treatment, AE related to CAD/LVD, deaths and hospitalisations in:
  - Patients receiving or not background beta-blockers at baseline
  - Patients with baseline HR ≥ / < 70 bpm
  - Patients with anginal pain at baseline / without anginal pain.
  - Patients with age ≥ / < 75 years
  - Patients with NYHA class I / class II / class III at baseline.
  - Men / women
- Analyses of emergent AEs and visual symptoms on treatment in patients with LVEF ≥ 35% / < 35%
- Analyses of lowest HR by class of HR in Safety Set and according to:
  - beta-blocker intake at baseline
  - Patients with baseline HR ≥ / < 70 bpm
  - Patients with anginal pain at baseline / without anginal pain
  - Men / women

- Event duration for recovered specific events: phosphenes, bradycardia, atrial fibrillation.

5.3.2.12 Protocol Amendments

Table 17. Protocol Amendments, BEAUTIFUL

	Important Changes
Initial protocol	
Amendment 1	9 February 2005 - global Minimum HR required for randomization increased from 55 – 60 bpm Minimum HR to up-titrate at Week 2 increased from 55 – 60 bpm Minimum HR to down-titrate the study drug dose in patients receiving 7.5 mg ivabradine twice daily was increased from 45 to 50 bpm Minimum HR to d/c drug in patients on 5 mg BID increased from 45 to 50
Amendment 2	16 March 2005 – UK only Administrative change of joint local sponsor
Amendment 3	03 January 2006 – all Holter centers Substudy objectives defined (b) (4) identified as the core lab Additional ICF incorporated
Amendment 4	03 January 2006 – all Echo/NT-proBNP centers Study objectives defined (b) (4) identified as core lab Additional ICF incorporated
Amendment 5	11 July 2006 – global DSMB changed to DMC Inclusion/Exclusion criteria maintained though not in agreement with the European Summary of Product Characteristics – justification included in this amendment CV SUSAR reporting ceased due to high frequency and unblinding of these events Change from paper to eCRF: software changed from INFORM to ORACLE RDC Endpoint “fatal and non-fatal myocardial infarction” deleted from endpoint list Definitions for used by Endpoint Validation Committee were clarified/completed
Amendment 6	22 January 2007 – global Follow up for last patients enrolled amended to 12 months for last patients due to higher than expected event rate for hospitalizations for new or WHF

5.3.3 SIGNIFY (also known as np33386 or CL3-16257-083)

Effects of ivabradine in patients with stable coronary artery disease without clinical heart failure - A randomized double-blind placebo-controlled international multicenter Study assessInG the morbi-mortality beNefits of the I_f inhibitor ivabradine in patients with coronary arterY disease (SIGNIFY).

5.3.3.1 Study Design and Objectives

SIGNIFY was an event-driven, phase III, international, multi-center, randomized, double-blind, placebo-controlled trial with two parallel and balanced treatment arms (ivabradine and placebo) in patients with stable coronary artery disease without clinical heart failure.

The trial consists of a run-in period of at least one week in which no placebo is given. The minimum study follow-up was 12 months.

Primary Objective: to demonstrate the superiority of ivabradine over placebo in the reduction of CV mortality or non-fatal myocardial infarction (MI) (composite endpoint).

Secondary Objectives: to assess the effect of ivabradine compared to placebo in the reduction of the non-composite endpoints, including all-cause mortality, CV mortality, coronary death (added by amendment No. 1), non-fatal MI, coronary revascularization (elective or not), elective coronary revascularization, new onset or worsening heart failure; as well as on other composite endpoints.

Other Objectives: to assess the change in angina symptoms using the classification of the Canadian Cardiovascular Society (CCS) in patients with angina symptoms at baseline; change in heart rate; and the assessment of safety.

5.3.3.2 Study Duration/Dates

Table 18. Important Dates in SIGNIFY

Final protocol completed	18 June 2009
First visit, first subject	25 September 2009
Amendment 1 global	08 June 2010
Amendment 2 global	14 June 2011
Amendment 3 – Saudi Arabia only	25 July 2011
Amendment 4 global	07 September 2012
Amendment 5 global	30 May 2013
Amendment 6 global	30 May 2013
Amendment 7 global	24 September 2013
Last visit, last subject	24 January 2014

SIGNIFY database lock	1 April 2014
SAP amended and finalized	1 April 2014
SIGNIFY treatment allocation unblinded	2 April 2014
Date of SIGNIFY final study report	21 August 2014

Reviewers comment: the SIGNIFY SAP was finalized the same day as database lock, and one day before allocation unblinding. There were changes to the SIGNIFY SAP the same day as database lock, one day before unblinding.

5.3.3.3 Study Sample Size and Power Considerations

From the SAP (20-21/508):

> *Initially, as stated in the final version of the study protocol dated 18 June 2009, 1 070 primary events and 11 330 patients (Machin & Campbell, 1987) were considered necessary to show a difference between the survival distributions of placebo and ivabradine groups, assuming a 5% type I error rate, a 90% power, an expected relative risk reduction of 18% and an annual incidence rate in the placebo group of 4.5% over a mean follow-up duration of 2.5 years (corresponding to 2 years of recruitment and 1.5 years of minimum follow-up). This sample size took into account the non-cardiovascular deaths and consent withdrawals (annual overall incidence of 1% for each event).*
>
> *During the study, an estimate of the incidence rate of primary events was performed when the data on the first 9500 randomized patients with 7-month follow-up have been collected into the database. This review was conducted in a blinded fashion based on data from treatment groups pooled that properly controlled the type I error rate of final analysis. From this blind assessment, the rate of primary events was deemed lower than anticipated and it was estimated that the number of events required for the primary endpoint will not be reached at the scheduled end of study. Therefore, based on an annual incidence rate in the placebo group estimated at 2.7% (corresponding to an overall incidence of 2.5% and a 18% relative risk reduction), the protocol amendment n°2, dated 14 June 2011, proposed to increase the sample size up to 16 850 patients and extend the recruitment period up to 2.5 years given a mean follow-up duration of 2.75 years.*
>
> *This review led to an increase in the sample size of this event driven trial but the targeted number of events was left unchanged, which hence, does not affect the type I error rate. Regarding the Randomized Set Angina (RSANG) of Symptomatic angina patients with class II or higher of the CCS classification at baseline, the proportion observed during this review in the overall population was equal to 60%. Assuming that this proportion would be maintained until the end of recruitment, it*

was estimated that this subgroup should finally gather approximately 10 100 patients. Based on a revised annual incidence rate of the primary composite endpoint of 3% in the placebo group for this subgroup and a mean follow-up duration of 2.75 years, this should approximately result in 710 events. This number of events will enhance the power close to 95% to detect the relative risk reduction defined in the protocol of 25%.

Actual enrollment was 19.102 patients with 9550 randomized to ivabradine and 9552 randomized to placebo.

5.3.3.4 Study Population

Key SIGNIFY Inclusion Criteria

- Male or female aged ≥ 55 years
- Evidence of CAD by either:
  - A previous MI (> 3 months prior to selection); or
  - Evidence of multivessel disease, irrespective of the revascularization status, i.e. either the presence of a significant stenosis (at least 50% narrowing of the luminal diameter), or a previous revascularization at least 3 months prior to selection (percutaneous transluminal coronary angioplasty with or without stent, or coronary artery bypass grafting) in 2 or more major coronary arteries [Note: A disease affecting the left main coronary artery was considered as a 2-vessel disease]; or
  - Evidence of non-revascularized single-vessel disease with the presence of angiographic evidence of at least 50% narrowing in one major coronary artery, plus either a positive non-invasive stress test, or a hospitalisation with a documented diagnosis of unstable angina (within 12 months prior to selection)
- Sinus rhythm and resting heart rate (HR) equal to or higher than 70 bpm on 2 consecutive resting 12-lead electrocardiograms (ECGs) performed at least 5 minutes apart
- LV ejection fraction of ≥ 41%
- Ambulatory and in stable condition with respect to angina and on appropriate and stable doses of conventional CV medications (≥ 1 month)
- Presence of additional CV risk factor(s):
  - At least one major risk factor:
    - Angina in CCS class II or higher (≥ 1 month):
    - Objective evidence of myocardial ischemia induced by stress testing (≤ 12 months prior to selection in patients who did not undergo subsequent coronary revascularization), either:
      - By a positive exercise tolerance test or

- Evidence of inducible myocardial ischemia with reversible abnormalities in at least two segments by any imaging technique.
- Hospital discharge with a documented diagnosis of major coronary event (acute MI or unstable angina) ≤ 12 months prior to selection

o At least two minor CV risk factors:
- Documented low HDL cholesterol (< 1 mmol/L or 40 mg/dL) and/or documented high LDL cholesterol (> 4 mmol/L or 160 mg/dL despite lipid lowering treatment)
- Type 1 or 2 diabetes mellitus treated with an oral hypoglycemic drug or insulin
- Documented peripheral artery disease (symptomatic or not); or angiographic evidence of significant (> 50%) peripheral artery stenosis in at least one limb; or evidence from a non-invasive measurement of significant peripheral artery stenosis in at least one limb
- Current smoker (10 cigarettes or more per day on average)
- Age ≥ 70 years

Key SIGNIFY Exclusion Criteria

- Transplanted heart
- Recent (less than 3 months) MI or coronary revascularization
- Stroke or cerebral transient ischemic attack within the preceding 3 months
- Scheduled for coronary revascularization procedures (PCI or CABG)
- Implanted pacemaker, implantable cardioverter defibrillator, cardiac resynchronization therapy
- Valvular disease likely to require surgery within the next 3 years
- Permanent atrial fibrillation or flutter
- Sick sinus syndrome, sino-atrial block, congenital long QT, 2nd degree and complete atrio-ventricular block
- Clinical signs and/or symptoms of heart failure in New York Heart Association (NYHA) class II or higher, or hospitalisation for heart failure as a primary diagnosis within the last 12 months.
- Known severe renal disease
- Known moderate or severe liver disease
- ALT or AST > 3 times the upper normal values
- Compliance with the study treatment < 70% during the run-in period
- Strong CYP3A4 inhibitors (e.g. macrolide antibiotics, antiretroviral drugs, azole antifungal agents administered by systemic route)

Key SIGNIFY Withdrawal Criteria

- Study drug not tolerated:
  - Symptomatic bradycardia
  - Low HR (< 50 bpm)

- Study drug no longer appropriate:
  - Prolonged loss of sinus rhythm

- Study Drug considered contra-indicated:
  - Pregnancy
  - Development of sick sinus syndrome or sino-atrial block
  - Concomitant administration of a strong cytochrome 3A4 inhibitors

Concomitant Treatments not Recommended

- Treatments that might prolong the QT (HR reduction my exacerbate QT prolongation)
- *Other negative chronotropes, about which the sponsor states the following: Amiodarone, diltiazem, verapamil and beta-blockers are likely to have an additive effect with the heart rate lowering effect of ivabradine. Patients on study treatment receiving open-label heart rate lowering medications and presenting with a HR consistently < 50 bpm on the resting standard 12-lead ECG or with signs or symptoms potentially related to bradycardia should have the study drug dose decreased (for patients receiving ivabradine 7.5 mg or 10 mg twice daily or matching placebo) or withdrawn (for patients receiving ivabradine 5 mg twice daily or matching placebo). The introduction of HR lowering agents (e.g. beta-blockers) after the randomization had to be clinically indicated. It was recommended to proceed with the introduction of such medications in progressive doses.*

5.3.3.5 Procedures

SIGNIFY Randomization

Randomization was centralized through an IRS, balanced between the two treatment groups, non-adaptive, and stratified on center (approximately 1150 center) and CCS class (no angina symptoms or class I / class ≥ II) at selection and inclusion.

SIGNIFY Treatments

Two resting ECGs at least 5 minutes apart were required for determining randomization eligibility based on HR criteria at baseline. Thereafter, the study treatment could be titrated up or down depending on HR (the lower of the 2 HR values measured from 2

ECGs recorded at each visit). The doses at randomization and at subsequent follow-up visits were to be managed as follows per protocol:

Randomization

- **In patients aged < 75 years at selection**, the starting dose was 7.5 mg ivabradine or matching placebo until the first follow-up visit (M1).
- **In patients aged ≥ 75 years at selection,** the starting dose was 5 mg ivabradine or matching placebo until the first follow-up visit (M1).

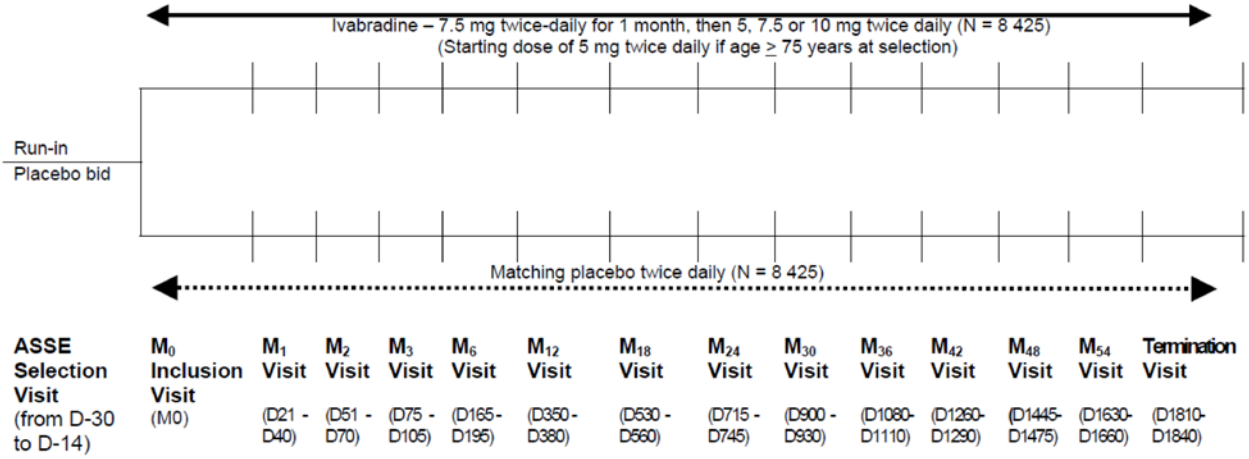
Titration

At the M1 visit and subsequent follow-up visits (or at any subsequent time between 2 scheduled visits), the study treatment could be titrated up or down depending on HR as follows:

- Maintain the study drug dose (for patients taking 5 mg or 7.5 mg or subsequently 10 mg ivabradine or matching placebo, twice daily), if ECG resting HR was ≥ 50 bpm and < 60 bpm and no signs or symptoms of bradycardia
- Adjust the dose to the next upper dose, (for patients taking 5 mg or 7.5 mg ivabradine or matching placebo, twice daily) provided that ECG resting HR was > 60 bpm and no signs or symptoms of bradycardia
- Adjust the dose to the next lower dose (for patients taking 7.5 mg or (subsequently) 10 mg ivabradine or matching placebo, twice daily) if ECG resting HR was < 50 bpm or if the patient was experiencing signs or symptoms related to bradycardia
- Stop the study drug (for patients taking 5 mg ivabradine or matching placebo, twice daily) if ECG resting HR was persistently < 50 bpm or if the patient was experiencing signs or symptoms related to bradycardia.

SIGNIFY Visit Schedule

Figure 16. SIGNIFY Schedule of Visits



Adapted from SIGNIFY SAP 19/508

SIGNIFY Schedule of Investigations

Figure 17. SIGNIFY Schedule of Investigations

Planned Time Scale	Selection from -30 days to -14 days	**Inclusion Day 0**	Month 1 D21–D40	Month 2 D51–D70	Month 3 D75–D105	Month 6 D165–D195	Month 12 D350–D380	Month 18 D530–D560	Month 24 D715–D745	Month 30 D900–D930	Month 36 D1080–D1110	Month 42 D1260–D1290	Month 48 D1445–D1475	Month 54 D1630–D1660	Month 60 D1810–D1840
Study Period	Run-in		Follow-up												
Study Treatment	Placebo single-blind		Double-Blind Active or Placebo Treatment												
Visit Name	Selection visit	**Inclusion visit**	Follow-up visits												Termination visit
Visit Code	ASSE	**M0**	M1 (f)	M2 (f)	M3 (f)	M6	M12	M18	M24	M30	M36	M42	M48	M54	TER
Information / Informed consent	x														
Selection / Inclusion criteria	x	**x**													
Concomitant treatments	x	**x**	x	x	x	x	x	x	x	x	x	x	x	x	x
Relevant medical history	x	**x**	x	x	x	x	x	x	x	x	x	x	x	x	x
Smoking habits	x	**x**					x		x		x		x		x
Clinical examination	x	**x**	x	x	x	x	x	x	x	x	x	x	x	x	x
Angina symptoms (CCS)	x	**x**	x	x	x	x	x	x	x	x	x	x	x	x	x
Class of heart failure (NYHA)	x	**x**	x	x	x	x	x	x	x	x	x	x	x	x	x
Height	x														
Weight	x	**x**			x		x		x		x		x		x
Waist circumference	x														x
Supine blood pressure	x	**x**	x	x	x	x	x	x	x	x	x	x	x	x	x
Resting standard 12-lead ECG/HR (2 consecutive recordings performed at least 5 minutes apart)	x	**x**	x	x	x	x	x	x	x	x	x	x	x	x	x
Left ventricular ejection fraction		**x** (c)													
Blood clinical lab. tests (b)		**x1** (d)			x2		x1		x1		x1		x1		x1(e)
Contact with the IRS	x	**x**	x	x	x	x	x	x	x	x	x	x	x	x	x
Study drug dispensation	x	**x**	x	x	x	x	x	x	x	x	x	x	x	x	
Safety assessment (a)	x	**x**	x	x	x	x	x	x	x	x	x	x	x	x	x
Compliance assessment		**x**	x	x	x	x	x	x	x	x	x	x	x	x	x

(a) Safety assessment including potential adverse events and pre-specified events occurred after the signature of the informed consent form.
(b) Blood clinical laboratory tests:
Type "x1": haemoglobin, haematocrit, red blood cell count, white blood cell count, platelet count, sodium, potassium, creatinine, ALT, AST, hsCRP (if feasible locally), fasting plasma glucose and fasting lipid profile (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol (calculated from the Friedewald's formula)).
Type "x2": sodium, potassium, creatinine, ALT, AST and hsCRP (if feasible locally).
(c) Results to be available before randomisation.
(d) Results to be available before randomisation. Samples could be taken during the selection visit, or between the selection visit and the inclusion visit.
***In centres participating to the ancillary studies implemented in a subset of countries,** additional investigations were performed at baseline and at different post-randomisation time points. These investigations were described in specific technical documents; these results were presented in separate study report.*
(e) Results to be available for the termination visit.
(f) The interval between M1 and M2 visits, as well as between M2 and M3 visits should not exceed 45 days.

Adapted from SIGNFIY SAP 19/508

SIGNIFY Premature Withdrawal

*If a **definitive discontinuation of the study treatment** was decided, the patient was asked to attend the next planned visits as previously scheduled until the study end, even if a PSE had already been reported. The aim was to let the investigator know whether subsequent PSE occurred in that patient and to collect other data, including safety parameters. All study procedures planned during the follow-up visits for patients receiving the study treatment were also carried out until the study end in patients having discontinued it, except prescription/dispensation of the study treatment and treatment compliance assessment. In the case of **treatment withdrawal due to an adverse event** (whether this event was subject or not to immediate notification), the investigator made every effort to collect the information relating to the outcome of the event. This information was recorded in the part of the e-CRF dedicated to adverse events. If the investigator could not organize a follow-up visit to collect this information, he / she had to collect it from the patient's treating physician. When the investigator had no news of a patient, he / she had to make every effort to contact him / her (unless the patient has clearly expressed his/her wish not to be contacted), to obtain the date when the study treatment was discontinued, to establish the reason for the discontinuation, to ask the patient to resume the study procedures or to suggest that he/she provided the contact details of his/her physician. The key study data (occurrences and dates of occurrences of the pre-specified events) were obtained from this physician when applicable.*
If all attempts to contact the patient failed – it was requested that all actions implemented were documented in the medical file – and if the key study data could not be obtained before the termination visit, the investigator declared the patient "lost to follow-up". (SIGNIFY FSR 36/225)

5.3.3.6 Efficacy Endpoints

Primary Composite Endpoint: Time to first CV death (including death of unknown cause and deaths of unclassifiable cause) and non-fatal MI

5.3.3.7 Safety Endpoints

- Time to first PCE components
- Time to first composite of Non-fatal MI and fatal MI
- Time to first elective coronary revascularization

5.3.3.8 Study Committees

Executive Committee

- *Composed of two Co-chairmen, (b) (4)*
- *Responsible for the development of the study protocol in collaboration with the sponsor. It advised the Steering Committee on possible changes in the study design and administration in order to guarantee achievement of the study main goal. It also advised the Steering Committee on stopping or modifying the trial (if applicable) and gave approval on the endpoint definitions and validation process produced by the Endpoint Validation Committee. It decided on the choice of ancillary studies in collaboration with the sponsor. It was mandated to plan and implement all publications, abstracts and presentations related to the study and advise the Steering Committee on this.*

Steering Committee

- *Chaired by (b) (4) and had as members the study national coordinators (i.e. the representative body of study investigators)*
- *Approved the protocol and the amendments of the study proposed by the Executive Committee, and reviewed the progress of the study*

Endpoint Validation Committee

- *Chaired by (b) (4)*
- *Responsible for the review and adjudication of the "pre-specified events" (PSEs) and it produced working definitions for the endpoints classifications that were approved by the Executive Committee.*

DMC

On the basis of efficacy and safety summaries and of formal interim analyses, the DMC made appropriate recommendations to the Executive Committee concerning the conduct of the study and supervised the safety aspects of the study.

- *Chaired by (b) (4) i.e. one statistician and four cardiologists.*
- *2 formal analyses performed but no changes to the study conduct were advised (there were no stopping rules in the case of futility).*

5.3.3.9 Identification of Potential Endpoint Events

Investigator Triggers (per the SIGNIFY protocol)

Pre-specified events (PSEs) were identified by the investigators and created a PSE file that enabled the EVC to adjudicate the events. The investigators collected the data required for the efficacy assessment (PSEs, if any, measurement of HR from resting ECG, and assessment of angina severity using the CCS functional classification). PSEs that were reviewed by the EVC were:

- All deaths.
- All suspected myocardial infarctions (leading to hospitalisation or not).
- All ischemic symptoms or any evidence suggestive of myocardial ischemia (other than stable angina) leading to hospitalisation (or prolongation of hospitalisation).
- All suspected strokes (leading to hospitalisation or not).
- Coronary revascularizations (PCI or CABG).
- All new onset or worsening of heart failure leading to hospitalisation (or prolongation of hospitalisation).

PSEs that occurred following consent withdrawal from the study were not reviewed by the EVC.

Automated Triggers for identifying PSEs

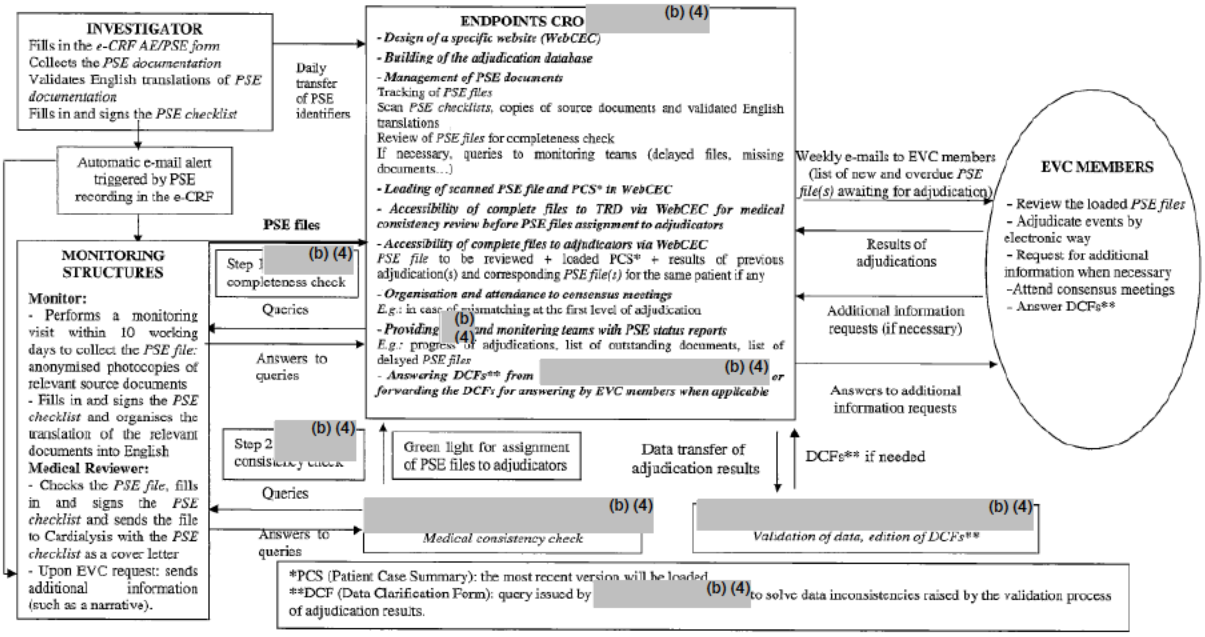
None identified.

5.3.3.10 Adjudication Process

Potential PSE events from SIGNIFY were sent to the Event Validation Committee (EVC) where level 1 adjudication was performed by three adjudicators. If there was not unanimous agreement on the adjudication by all three, the potential PSE was referred for second level adjudication. Final adjudication results reflected the majority opinion at consensus meetings.

The communication flows between the EVC members and the other structures of the SIGNIFY study as shown in the following diagram:

Figure 18. Communications Flows within SIGNIFY



Adapted from SIGNIFY EVC Charter 9.34

5.3.3.11 Statistical Analysis Plan

On 1 April 2014, the day the database was locked, the SAP was amended as follows (from the addendum to the SAP dated 1 April 2014):

- In order to take into account the multiplicity of secondary endpoints, a hierarchical procedure testing was performed for two major secondary endpoints starting with the composite of Non-fatal MI and fatal MI and followed by elective coronary revascularization. Other secondary endpoints were considered as supportive or exploratory, and thus no adjustment for multiplicity was applied for these endpoints.
- Subgroups were defined for the primary endpoint:
  - PAD (yes/no)
  - Previous MI (yes/no)
  - Hypertension (yes/no)
  - Hypercholesterolemia (yes/no)
  - Diabetes (yes/no)
  - Sedentary lifestyle (yes/no)
  - Obesity (yes/no)
  - Smoking (yes/no)
  - Heart rate (bpm)
  - Age (years)

  - Gender (Male/Female)
  - CCS class (< II / ≥II)
- The secondary analyses described in the protocol for the primary endpoint was also performed on its components and on all-cause mortality.
- The treatment effect was also estimated and tested, as a secondary analysis, using an unadjusted Cox's proportional hazard model, for the primary composite endpoint and all secondary endpoints.
- Evolution of grade of angina pain from baseline (Improvement/Stability/Worsening) was described at M003 and last value. Estimates and 95% confidence interval of the difference between treatment groups of improvement rate was also be provided.
- All planned efficacy analyses (main, secondary and sensitivity) focus on endpoints confirmed by the Endpoint Validation Committee, as considered to be the most reliable and homogeneous assessment. Therefore, analyses of events that occurred after consent withdrawal and retrieved from different sources will be performed as post-hoc sensitivity analyses.

5.3.3.12 Protocol Amendments

Table 19. Protocol Amendments, SIGNIFY

	Important Changes
Amendment 1 global	08 June 2010 Secondary efficacy endpoint of "coronary death" added e-CRF modified with more details for coronary disease Definition of excessive intake of drug updated Biomarkers of CAD sub-study added in select countries No changes to ICF
Amendment 2 global	14 June 2011 Increase randomized patients to 16,850 Follow-up period extended to 48 months Clarify cardiac meds must be table during run-in Required updated ICF from all patients
Amendment 3 – Saudi Arabia	25 July 2011 Non-Substantial
Amendment 4 global	07 September 2012 Updated con-med precautions (diuretics) Updated list of AEs for which special info requested Definitions of AE intensity clarified ICF was amended
Amendment 5 global	30 May 2013 To minimize the number of patients missing follow-up information of vital status and hospitalisations for CV events at the end of the study. Applicable to all countries where it was permitted to retrieve, for patients who withdrew consent, their vital status. May have required an amended

	ICF.
Amendment 6 global	30 May 2013 To minimize the number of patients missing follow-up information of vital status and hospitalisations for CV events at the end of the study. Applicable to all countries where it was permitted to retrieve, for patients who withdrew consent, their dates of CV hospitalizations. May have required an amended ICF.
Amendment 7 global	24 September 2013 Non-substantial

5.3.3.13 Overall SIGNIFY Results and subgroup with EF < 50%

Table 20. SIGNIFY Published Analysis: PCE and Components

	Ivabradine (N=9550) n (%)	Placebo (N=9552) n (%)	HR (95% CI)	p-value
Primary Composite Endpoint	COPYRIGHT MATERIAL WITHHELD IN FULL (Fox K et al N Engl J Med 2014: 371:5)			
Secondary Endpoints				
Cardiovascular Death				
Nonfatal MI				
Death from Any Cause				

[Source: Fox K et al. N Engl J Med 2014. DOI: 10.1056/NEJMoa1406430]

Reviewer comment: Our analysis of subjects with EF<50% suggests that there is not increased harm due to ivabradine in these subjects.

Table 21. SIGNIFY primary composite endpoint by subjects with EF< 50%, ≥50%

Entire randomized population									
Subgroup	Ivabradine N=9550			Placebo N=9552					
	n/N	%	%PY	n/N	%	%PY	RR (95% CI)		Interaction p-value
Baseline EF < 50%	199 / 2088	(9.5)	4.3	199 / 2094	9.5	4.2	1.02	(0.84, 1.24)	0.492
Baseline EF ≥ 50%	450 / 7371	(6.1)	2.7	406 / 7356	5.5	2.4	1.11	(0.97, 1.27)	
Angina Subgroup									
	Ivabradine N=6037			Placebo N=6012					
Baseline EF < 50%	146 / 1435	(10.2)	4.6	136 / 1446	(9.4)	4.2	1.10	(0.87, 1.39)	0.452
Baseline EF ≥ 50%	311 / 4558	(6.8)	3.0	251 / 4510	(5.6)	2.5	1.23	(1.04, 1.45)	

Reviewer's analysis: SIGNIFY\data\nb_pce_subgroup

6 Review of Efficacy

Efficacy Summary

This NDA is submitted for the approval of ivabradine, an HCN4/I_f Channel blocker that slows the heart rate by slowing the discharge rate of the sinus node, to reduce the risk of cardiovascular mortality or hospitalizations for worsening heart failure in patients with chronic heart failure (b) (4) with systolic dysfunction and in sinus rhythm with heart rate ≥ 70 beats per minute (bpm), (b) (4) including maximally tolerated doses of beta-blockers or when beta-blocker therapy is contraindicated (b) (4) Its evaluation during this review is based on the efficacy data from a large single cardiovascular outcome study, SHIFT (also known as np29800 or CL3-16257-063), that was conducted completely outside of the US, as were all of the pre-phase 3 support studies and another large Phase 3 CV outcomes trial in a somewhat different population, BEAUTIFUL (AKA NP27426 or CL3-16257-056) that is being used supportively. None of these trials were conducted under a US IND.

The SHIFT study was an event driven trial, testing ivabradine as add-on therapy to standard medical therapy of Heart Failure with Reduced Ejection Fraction (HFrEF). It was conducted from 2006 to 2010, an era during which standard medical practice for the treatment of HFrEF was similar, if not identical, to current standards of medical practice for this condition (with the exception of a somewhat of a narrowing of the indications for certain device therapies). SHIFT enrolled a very sick population of patients: subjects with Left Ventricular Ejection Fractions (LVEF) $\leq$ 35%, NYHA CHF classes II-IV (mostly II-III), and a resting heart rate $\geq$ 70 bpm, on optimal background pharmacologic therapy to include the specific beta-blockers that were recommended at the time per the ESC-guideline for treating HF, and specifically guideline-directed target doses of these beta-blockers. ACE inhibitors and/or ARBs, as well as aldosterone antagonists and diuretics were likewise to be optimized. The primary composite outcome of SHIFT was CV Death or Hospitalization for Worsening Heart Failure (WHF).

It has been known for quite some time that HFrEF patients with the highest resting heart rates have the worst outcomes. The SHIFT trial was essentially testing the hypothesis that for HFrEF patients with persistently elevated heart rates on guideline directed beta-blockers (or the highest dose of beta-blocker that could be used if the target beta-blocker doses could not be achieved due to patient intolerance, or could not be used at all), that slowing their heart rates would confer a survival and/or hospitalization advantage versus placebo. Indeed, the SHIFT results are compelling, demonstrating a p-value for the point estimate of the hazard ratio for the occurrence of its primary composite endpoint, CV death and/or Hospitalization for WHF, which is essentially zero, as shown in the table below:

Table 22. FDA SHIFT Analysis: Primary Composite Endpoint, RS

Analysis Sets	Ivabradine		Placebo		HR (95% CI)	p-value
	n/N	%	n/N	%		
RS						
PCE	793/3241	24.5	937/3264	28.7	0.82 (0.75, 0.90)	<0.0001
CV Death	449/3241	13.9	491/3264	15.0	0.91 (0.80, 1.03)	0.128
Hospitalization for WHF	514/3241	15.9	672/3264	20.6	0.74 (0.66, 0.83)	<0.0001

This striking result in the PCE is, as expected, driven by hospitalization for WHF, but there is a non-statistically significant lean toward a benefit in CV mortality as well. This result in the PCE of SHIFT is supported by a series of nominally beneficial effects of ivabradine across a series of secondary endpoint outcomes as follows:

- death from heart failure (hazard ratio: 0.74; 95% CI: [0.58, 0.94]; p = 0.014)
- all-cause hospitalization (0.89; [0.82, 0.96]; p = 0.0027)
- hospitalization for a cardiovascular reason (0.85; [0.78, 0.92]; p = 0.0002)
- Hospitalization for worsening heart failure (0.74; [0.66, 0.83]; p < 0.0001).

There were also leans toward benefit from other secondary endpoints as follows:

- All-cause mortality (0.90; [0.80, 1.02]; p = 0.092)
- Cardiovascular death (0.91; [0.80, 1.03]; p = 0.128).

While these impressive death and hospitalization benefits were reported by the sponsor, they were verified by FDA analyses of the submitted datasets, as follows:

Table 23. FDA SHIFT Analysis: Treatment Effect on Causes of death, RS

	Hazard Ratio (95% CI)	p-value
Death from any cause	0.90 (0.80, 1.02)	0.092
Cardiovascular death	0.91 (0.80, 1.03)	0.128
Sudden cardiac death	1.05 (0.87, 1.26)	0.630
Death from heart failure	0.74 (0.58, 0.94)	0.014
Non-cardiovascular death	0.87 (0.60, 1.25)	0.455

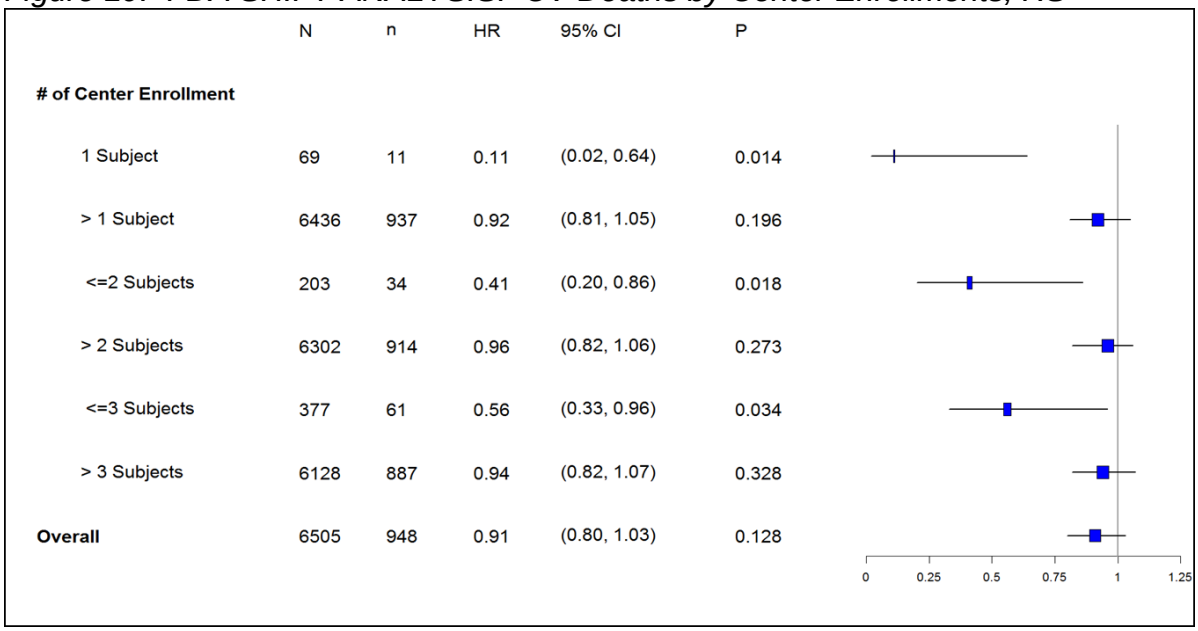
Table 24. FDA SHIFT Analysis: Estimates of Treatment Effect on Causes of Hospitalization, RS

	Hazard Ratio (95% CI)	p-value
Hospitalization from any cause	0.89 [0.82, 0.96]	0.0027
Hospitalization from CV reason	0.85 [0.78, 0.92]	0.0002
Hospitalization from WHF	0.74 [0.66, 0.83]	<0.0001
Unplanned hospitalization for any cause	0.88 [0.81, 0.95]	0.0013
Unplanned hospitalization for CV reason	0.84 [0.77, 0.92]	0.0002

Robustness of the Overall SHIFT Efficacy Results

There was no site, country, or region that was statistically influential in driving the SHIFT results. Indeed, completely removing the two highest enrolling countries, Russia and Ukraine, did not change the overall SHIFT results. It was noted early in the review that there were a cluster of sites that enrolled only a single patient, and that the estimate for the hazard ratio of CV death among this cluster of sites was 0.11, and statistically different from the results of sites enrolling more than 1 subject, as shown in the figure below:

Figure 19. FDA SHIFT ANALYSIS: CV Deaths by Center Enrollments, RS



This finding would have been concerning had it involved the hospitalization for WHF component of the primary composite, as the argument could have been made that sites may have been partially unblinded by the measureable heart rate decrease in the patients

on active therapy during SHIFT, and somehow this may have influenced the decision to admit or not to admit to the hospital for WHF. However, this result occurred for the CV mortality outcome, and vital status follow up in this trial was very good. Furthermore, if one takes these 69 sites, identifies them as a "region", and then completely removes them from the SHIFT efficacy analysis, the overall result of the SHIFT trial does not change. Accordingly, the alternative explanations for this finding is that it either occurred as a chance finding among a small group of sites, or that low enrolling sites may also have been sites that had less rigorous use of beta-blockers, a group for which ivabradine appears to work especially well (see section 6.1.6).

Finally, analysis of the SHIFT PCE, its components of CV death and hospitalization for WHF, as well as for all-cause mortality, as a function of baseline HR, all show point estimates for the hazard ratio of treatment effects to be less than 1 for all heart rates above 70 (section 6.1.7).

SHIFT Sub-studies

There were four sub-studies in SHIFT, all of which suggested favorable effects or at least the absence of harm for ivabradine therapy as follows (see section 6.10 for details):

1. SHIFT Echocardiography: In this substudy of 411 patients (208 on ivabradine, 203 on placebo) comparing echo results at month8 to baseline echos, nominally significant reductions of LVESVI, LVEDVI, LVESV, and LVEDV, and an increased LVEF relative to placebo were measured.

2. SHIFT NT-proBNP: In this substudy of 525 patients (268 on ivabradine, 257 on placebo), the ratio of the geometric means for last value / baseline was lower for Ivabradine patients than for controls.

3. SHIFT-PRO: In this substudy of 4036 subjects (N=2018 ivabradine, N=2018 placebo), the primary endpoint was the placebo adjusted change from baseline of the Visual Analogue Scale (EQ VAS) of the EuroQoL questionnaire (EQ-5D, 0 (worst) to 100 (best)). This outcome was not different between the two treatment arms. The secondary efficacy endpoint of this substudy was the KCCQ clinical summary score. Substitution for death consisted in setting the last-post-baseline value to 0 for deceased patients. The mean KCCQ Clinical summary score baseline value was 68.7 ± 20.0 in the ivabradine group and 68.1 ± 20.6 in the placebo group. Mean KCCQ Clinical summary score decreased between baseline and last post-baseline value in both treatment groups. But the decrease was significantly higher for the placebo group than for the ivabradine group, with an estimated difference significantly in favor of ivabradine by 3.28 ± 1.30, ($p<0.05$).

4. SHIFT Holter: In this substudy of 602 patients(298 on ivabradine and 304 on placebo), centrally interpreted Holter monitors (core lab – (b) (4) for ivabradine-treated patients, as compared to placebo-treated patients, demonstrated
    a. An increase in all heart rate variability (HRV) time domain parameters (the difference between groups in mean increase from baseline was significant (main analysis) for all parameters)
    b. Improvement in total power as well as power in all frequency ranges for the analysis of frequency domain parameters (difference between groups in mean change (main analysis) was significant)
    c. At M008, the percentage of patients with TO and TS normal was higher in the ivabradine group than in the placebo group (43.3% *versus* 38.7%, respectively) whereas the opposite was observed at baseline (38.1% in the ivabradine group *versus* 44.2% in the placebo group)
    d. In the ivabradine group, the mean of lowest HR at M008 over 24-hour period was 45.3 ± 7.0 bpm compared to 50.8 ± 8.3 bpm in the placebo group
    e. In the ivabradine group, the mean of highest HR at M008 was 117.9 ± 23.6 bpm compared to 125.3 ± 22.3 bpm in the placebo group over 24-hour period
    f. Bradycardia < 50 bpm in term of lowest HR during episodes was similar in both groups: median was 42 bpm at M008 in the ivabradine group and 45 bpm in the placebo group, minimum HR during these episodes was 33 bpm in the ivabradine group and 31 bpm in the placebo group
    g. At M008, bradycardia < 40 bpm were mainly reported during sleep period: 18.5% in the ivabradine group versus 9.1% during awake period.
    h. No patient had bradycardia with HR < 30 bpm at M008
    i. There were more patients with pauses > 2 sec at M008 in the ivabradine group than in the placebo group irrespective of the period (8.7% versus 3.6% over 24-hour period) but there was no difference regarding pauses > 2.5 sec (1.2% versus 1.6% in ivabradine and placebo groups, respectively). Furthermore, no patient experienced a pause > 3 sec in the ivabradine group.
    j. The percentage of patients with supraventricular tachycardia (SVT) at M008 was slightly higher in the ivabradine group (43.7%) than in the placebo group (41.3%): for all patients except two in the ivabradine group, SVT were non-sustained. However, considering only SVT occurring on treatment, there was no difference between groups (40.9%). The change in number of episodes of non-sustained SVT was in median equal to 0 in both groups.
    k. No sustained ventricular tachycardia (VT) was reported on the Holters recording at M008 over 24 hours. Patients with non-sustained ventricular tachycardia at M008 were less frequent in the ivabradine group (28.4%) than in the placebo group (33.2%). The percentage of patients with polymorphic VT was slightly higher in the ivabradine group (11.0%) than in the placebo group (9.7%) at M008 but this frequency imbalance was already present at baseline (14.6% versus 13.5%, respectively).

l. At M008, atrial fibrillation (AF) was reported in 6 patients (2.4%) in the ivabradine group (2 of them were not under treatment) and in 5 patients (2.0%) in the placebo group (3 of them were not under treatment and one already experienced AF on the Holter recording at baseline) over 24 hours.
m. In the ivabradine group, 22.1% of the patients had accelerated idioventricular rhythm (AIVR) over 24 hours at M008 versus 19.8% in the placebo group (same trend was observed at baseline: 20.1% versus 19.1%, respectively).

Support from BEAUTIFUL post-hoc subgroups

BEAUTIFUL was a large, multi-center, randomized, double-blind, placebo-controlled, phase 3 outcomes study in 10,946 subjects (10,917 evaluable subjects) with stable CAD and left ventricular dysfunction. Its primary objective was to demonstrate the superiority of ivabradine over placebo in the reduction of incidence of the composite endpoint: cardiovascular (CV) mortality, hospital admissions for acute myocardial infarction (MI), hospital admissions for new onset or worsening heart failure (HF). BEAUTIFUL enrolled a lower risk population than SHIFT – patients with heart rates as low as 60 bpm, documented CAD a mean ejection fraction of 34% (as opposed to 29% in SHIFT), stable clinical symptoms for at least 3 months, and no requirement for hospitalization for WFH in the prior year. For convenience, the following table compares and contrasts SHIFT and BEAUTIFUL side by side:

Table 25. Design Differences, SHIFT vs BEAUTIFUL

	SHIFT (pivotal)	BEAUTIFUL (support)
N	6,558 (efficacy - benefit)	10,917 (efficacy – none)
Duration	09/2006 – 04/2010	12/2004 – 02/2008
Population	Mean ivab age 60.7 yrs CHF in SR LVEF ≤ 35% NYHA CHF Class II-IV rHR > 70	Mean ivab age 65.3 yrs Documented CAD in SR LVEF ≤ 39% Stable CAD/CHF Sx rHR > 60
Ivabradine Treatments	Placebo vs. Ivabradine 2.5, ***5*** or 7.5 mg BID	Placebo vs. Ivabradine ***5*** or 7.5 mg BID
Ivabradine Mean Dose	6.4±1.4 mg BID	6.18±1.25 mg b.i.d. (RS) 6.64±1.25 mg b.i.d. (RS_{HR70})
HR Target	50 – 60	50 – 60
Mean HR	~65 bpm @ 3 mos (ivab) ~75 bpm @ 3 mos (placebo)	~ 61 bpm @ 3 mos (ivab) ~ 70 bpm @ 3 mos (Placebo)
Endpoint	Time To CV death or hospitalization for WHF	Time to CV death, hosp for AMI, hosp for new onset or WHF

BEAUTIFUL failed to meet its primary endpoint, specifically showing benefit for neither CV death (which actually leaned toward harm) nor hospitalization for new onset or WFH, per the following table of BEAUTIFUL outcomes:

Table 26. FDA BEAUTIFUL Analysis: Incidence of PCE and Components

	Ivabradine (N=5479) n (%)	Placebo (N=5438) n (%)	HR (95% CI)	p-value
Primary Composite Endpoint	844 (15.4)	832 (15.3)	1.00 (0.91, 1.10)	0.945
Secondary Endpoints				
Cardiovascular Death	469 (8.6)	435 (8.0)	1.07 (0.94, 1.22)	0.316
Hospitalization for acute MI	199 (3.6)	226 (4.2)	0.87 (0.72, 1.06)	0.159
Hospitalization for new onset or Worsening Heart Failure	426 (7.8)	427 (7.9)	0.99 (0.86, 1.13)	0.850
	N=2699	N=2693		
Hospitalization for acute MI in RS-HR70*	85 (3.2)	131 (4.9)	0.64 (0.49, 0.84)	0.001

[Source: Sponsor's CSR np27426-01 Table (11.1.1) 1, confirmed by the reviewer
* **RS-HR70** is randomized set of patients with baseline hear rate 70 bpm or more]

However, the sponsor went back to the BEAUTIFUL datasets to identify two progressively more "SHIFT-like" populations as follows for the purpose of conducting post-hoc analyses on the BEAUTIFUL efficacy data using the SHIFT primary composite endpoint:

1. BEAUTIFUL patients with class II/III NYHA and HR $\geq$ 70 BPM
2. BEAUTIFUL patients with class II/III NYHA and HR $\geq$ 70 BPM, now super-selected to have average baseline characteristics more similar to the population in SHIFT (considering NYHA class, LVEF, baseline HR, prior MI). Of note, there was no information on hospitalizations for WHF because this was not collected in BEAUTIFUL. This subpopulation was called the "Calibration Subpopulation."

The results of analyzing these two progressively more "SHIFT-like" groups from BEAUTIFUL for the SHIFT PCE produced statistically significant results per the following tables, which the applicant submits as supportive data for the overall SHIFT outcome (from applicant's clinical overview p 57):

Table 27. Post Hoc BEAUTIFUL Sub-population (NYHA Class II/III and HR ≥ 70 bpm) Analysis for SHIFT PCE and Components

	BEAUTIFUL NYHA Class II/III and HR ≥ 70 bpm Subpopulation					
	Ivabradine (N = 1684)		Placebo (N = 1679)		Hazard Ratio	P-value[c]
	n (%)	%PY	n (%)	%PY	E (95% CI)[b]	
Primary composite endpoint[a]	314 (18.7)	12.5	332 (19.8)	13.5	0.93 (0.80 ; 1.08)	0.3438
Component endpoints						
Cardiovascular death	199 (11.8)	7.5	193 (11.5)	7.3	1.03 (0.84 ; 1.25)	0.7767
Hospitalization for worsening heart failure	197 (11.7)	7.8	214 (12.8)	8.7	0.90 (0.74 ; 1.10)	0.2998

Table 28. Post Hoc BEAUTIFUL Sub-population (Calibration) Analysis for SHIFT PCE and Components

	BEAUTIFUL Heart Failure Calibration Subpopulation					
	Ivabradine (N = 592)		Placebo (N = 611)		Hazard Ratio	P-value[c]
	n (%)	%PY	n (%)	%PY	E (95% CI)[b]	
Primary composite endpoint[a]	116 (19.6)	13.3	151 (24.7)	17.4	0.77 (0.60 ; 0.98)	0.0309
Component endpoints						
Cardiovascular death	77 (13.0)	8.4	87 (14.2)	9.2	0.91 (0.67 ; 1.24)	0.5692
Hospitalization for worsening heart failure	73 (12.3)	8.4	104 (17.0)	12.0	0.70 (0.52 ; 0.94)	0.0191

Key Issues with the efficacy clinical trials

No program data for supporting efficacy is flawless, and this one is no exception. The list of concerns

- Method to control for multiplicity among the numerous secondary endpoints was not clear to the reviewer from the statistical analysis plan. This will be further explored with FDA biometrics and the sponsor.

- For both SHIFT and BEAUTIFUL, the statistical analysis plan was finalized after database lock, but before unblinding of the data. While there is always the concern that knowledge of the results of an ongoing trial may have influenced the statistical analysis plan when the latter are finalized after all the enrollment has long been completed, this practice was more common in the era that these trials were conducted, and it certainly cannot be concluded that this in any way helped the BEAUTIFUL results, as this trial failed to meet it pre-specified primary endpoint.

- There is an apparent inconsistency between BEAUTIFUL and SHIFT. However, these were different populations of patients, with the SHIFT population being much sicker with a higher exposure-corrected event rate, with BEAUTIFUL focusing more on the stable ischemic heart disease with left ventricular dysfunction and SHIFT focusing more on sicker HF patients . While the BEAUTIFUL post-hoc sub-analyses have their limitations, the fact remains that in selecting the most SHIFT-like patients from BEAUTIFUL and then analyzing them for the SHIFT primary composite endpoint, a statistically significant and positive treatment effect of Ivabradine is apparent.

- The PCE of SHIFT was CV death and hospitalization for WHF. The hospitalization for WHF component of the PCE drove the efficacy result. Were the trial to be functionally unblinded, the decision of whether to admit or not admit patients for WHF could have been biased to show drug effect. The argument can be made that SHIFT was indeed at least partially unblinded, since ivabradine patients would have demonstrated decreased heart rates (sometimes dramatically so). However, there was broad overlap in the day 28 heart rate histograms for the two treatment arms that would have made a systemic manipulation of the trial results on this basis alone very difficult, especially given the very profound treatment effect that was demonstrated in the overall trial (p-value essentially zero).

Limitations of the Applicability of the Efficacy Data

- Ivabradine demonstrates rate dependence of I_f blockade. Accordingly, concomitant therapy with other negative chronotropes appears to blunt the clinical effect of ivabradine (no significant benefit in patients taking at least 50% of target doses of guideline-directed beta-blockers or digoxin, section 6.1.7).

- SHIFT is essentially a trial of combination negative chronotropes (ivabradine ± beta-blockers ± digoxin ± Amiodarone). Luckily, HFrEF patients do not generally take non-DHP CCBs which could also drop heart rate synergistically in the setting of ivabradine therapy. SHIFT tightly controlled background negative chronotropes at baseline (stable BB dose, stable CHF meds, and so stable dig dose as well), then initiated ivabradine on a background of stable negative chronotropic therapy. (b) (4)

[redacted] (b) (4)

- [redacted] (b) (4) The results of this composite endpoint were driven by hospitalizations for WHF. Indeed, the sponsor notes that, "the incidence of at least one hospitalisation for MI was similar in the 2 groups (2.6% versus 2.7%, ivabradine vs placebo, respectively).

- The use of devices with proven efficacy for the reduction of CV death and/or hospitalization for worsening heart failure as background therapy in SHIFT did not and does not reflect contemporary US practice. For example, for patients with a LVEFs < 35% and LBBB (QRS > 150 msec, NYHA class > II), CRT therapy carries a class-I recommendation in the 2012 ACCF/AHA/HRS Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities, and has been shown to reduce hospitalizations and mortality. It is unclear that ivabradine would confer any additional mortality and/or hospitalization benefit in the CRT or CRT-D treated population. For those patients without LBBB, ICD therapy would be indicated in the US for most all for the reduction of mortality (class I recommendation, LVEF < 35% and NYHA II-III, or IHD with LVEF < 30% and NYHA I).

  This being said, there is no reason to think that patients with an ICD (without CRT) would not derive the same benefit from ivabradine as did patients in SHIFT. Furthermore, had devices been allowed in SHIFT, the myriad permutations of ICD only, CRT, CRT-D, programming modalities, and drug-device interactions could have made the interpretation of the trial for drug effect extremely difficult. For example, in patients with CRT devices programmed with a lower rate limit of 60 bpm or higher, ivabradine would likely have caused these patients to become pacemaker dependent as a function of the programmed lower rate limit of their devices. This would have resulted in ivabradine dose escalation to the maximum permitted 7.5 mg BID dose in these patients, with their CRT device determining their ivabradine dose, as opposed to their sinus rate serving as a biological marker for dose escalation.

- The SHIFT result was driven by hospitalization for WFH, and SHIFT was conducted completely outside of the United States, not under an IND. In approving ivabradine for the CHF indication in the United States, the assumption must be made that ascertainment of WHF in SHIFT, and the decision to hospitalize WHF in SHIFT, are applicable to WHF hospitalization practices in the US, which are changing dramatically at this time to include in-clinic treatment of exacerbations of heart failure that were formally admitted to hospital.

- Ivabradine demonstrates rate dependence of I_f blockade. Accordingly, concomitant therapy with other negative chronotropes appears to blunt the clinical effect of ivabradine (no significant benefit in patients taking at least 50% of target doses of guideline-directed beta-blockers or digoxin, section 6.1.7).

The Reviewer's Efficacy Conclusions

- The SHIFT primary endpoint composite outcome is compelling and robust. The findings lend credence to prior assessments that suggested that lowering heart rate in HFrEF patients may be the mechanism of benefit in HFrEF patients treated with beta-blockers.

- Many patients cannot tolerate beta-blockers, or cannot tolerate guideline-directed target doses of beta-blocker. At randomization in SHIFT, reasons included COPD, hypotension, asthma, fatigue, Raynaud's phenomenon or PAD, dizziness, AV block, metabolic disorders, sexual dysfunction, dizziness, and cardiac decompensation. Ivabradine could offer a welcomed addition to the armamentarium for the treatment of these HFrEF patients.

- (b) (4)

- US practice regarding hospital admission of WHF is changing. However, it is the opinion of this reviewer that hospitalization for WHF is a surrogate for physiologic deterioration. Thus, it could be reasonably expected that engagement of the medical system for intervention in WHF will be decreased in the US regardless of whether that is manifest as hospital admissions or intensive clinic visits during which intravenous medications are administered.

6.1 Indication (proposed)

To reduce the risk of (b) (4) hospitalizations for worsening heart failure in patients with chronic heart failure (b) (4) with systolic dysfunction and in sinus rhythm with heart rate ≥ 70 beats per minute (bpm), (b) (4) including maximally tolerated doses of beta-blockers or when beta-blocker therapy is contraindicated (b) (4)

6.1.1 Methods

Approval is sought for the indication noted above based on SHIFT: a single, large trial assessing CV mortality and hospitalizations in a group of patients with moderate to severe symptomatic heart failure with measured left ventricular ejection fractions (LVEF) ≤ 35%

(for a complete description of the trial, see section 5.3.1 and its labeled sub-sections. SHIFT met its primary endpoint with a p-value that was essentially zero: the time to first occurrence of cardiovascular death or hospitalization for worsening heart failure. The following sub-sections will focus on the SHIFT trial.

The sponsor also submitted the BEAUTIFUL trial in support of this application. BEAUTIFUL did not meet its primary endpoint, but there were substantial differences between BEAUTIFUL and SHIFT. BEAUTIFUL was conducted in parallel with SHIFT, though it was concluded in advance of SHIFT. BEAUTIFUL was a large outcome trial in patients with moderate to severe LV dysfunction that only enrolled patients with ischemic cardiomyopathies (all patients had CAD). The heart rate entry criteria for BEAUTIFUL was lower than for SHIFT (60 versus 70 bpm), an important distinction in testing an I_f blocker that demonstrates use dependence during voltage clamping. Patients in BEAUTIFUL appeared to have less severe HFrEF overall than SHIFT patients, with inclusion of patients with LVEFs $\leq$ 39%, and a mean LVEF in the Group of 34%. The primary endpoint of BEAUTIFUL was different: the time to first occurrence of cardiovascular mortality, hospital admission for acute myocardial infarction, or hospital admission for new onset or worsening heart failure. However, two post-hoc sub-group analyses of BEAUTIFUL's progressively more "SHIFT-like" patients (lower ejection fractions with more symptomatic heart failure and matched to SHIFT demographics) did mirror the overall findings of shift – a reassuring finding. For a detailed description of BEAUTIFUL, see section 5.3.2 and its labeled subsections. BEAUTIFUL's post-hoc subgroup results are discussed in the section 6 efficacy summary above.

Finally the SIGNIFY trial datasets were submitted earlier this month so that further analyses might be accomplished on potential drug-interactions with loop diuretics. Briefly, SIGNIFY was the largest of the ivabradine Phase III trials to date. SIGNIFY assessed a completely different population of patients (stable CAD without symptomatic CHF symptoms, an LVEF $\geq$ 41% per protocol, a mean LVEF of 56% for the group), taking a higher dose range of ivabradine than was used in SHIFT (5mg, 7.5 mg and 10 mg BID as opposed to 2.5 mg, 5.0 mg, and 7.5 mg BID, respectively). SIFNIFY's primary endpoint was likewise unique: CV mortality and non-fatal MI. The overall CV outcome analysis of SIGNIFY was neutral. Because this trial enrolled substantially different patients, tested a different dosing algorithm, and measured a different primary endpoint, it will not be further discussed here in section 6, but a full summary of its design elements and overall results is presented in section 5.3.3 and its labeled subsections. Pertinent elements of CV subgroup safety relating to the dose, lower heart rates achieve, and unique con-med background therapy from SIGNIFY is discussed in the section 6 efficacy summary above.

A summary of similarities and differences between SHIFT, BEAUTIFUL, and SIGNIFY is presented in the table below, with the doses rendered in ***bold-underlined-blue italics*** representing the starting doses in the three different trials:

Table 29. Design Comparison, SHIFT vs BEAUTIFUL vs SIGNIFY

	SHIFT (pivotal)	BEAUTIFUL (support)	SIGNIFY
N	6,558 (efficacy - benefit)	10,917 (efficacy – none)	19102 (efficacy - ? none)
Duration	09/2006 – 04/2010	12/2004 – 02/2008	9/2009 – 1/2014
Population	Mean ivab age 60.7 yrs CHF in SR LVEF ≤ 35% NYHA CHF Class II-IV rHR > 70	Mean ivab age 65.3 yrs Documented CAD in SR LVEF ≤ 39% Stable CAD/CHF Sx rHR > 60	Mean ivab Age 65.0 yrs Stable CAD in SR LVEF > 40% NYHA CHF Class 1 rHR ≥ 70
Ivabradine Treatments	Placebo vs. Ivabradine 2.5, **5** or 7.5 mg BID	Placebo vs. Ivabradine **5** or 7.5 mg BID	Placebo vs. Ivabradine 5, **7.5**, or 10 mg BID
Ivabradine Mean Dose	6.4±1.4 mg BID	6.18±1.25 mg b.i.d. (RS) 6.64±1.25 mg b.i.d. (RS_{HR70})	8.2±1.7 mg BID
HR Target	50 – 60	50 – 60	55-60
Mean HR	~65 bpm @ 3 mos (ivab) ~75 bpm @ 3 mos (placebo)	~ 61 bpm @ 3 mos (ivab) ~ 70 bpm @ 3 mos (Placebo)	60.7±9.0 bpm (ivab-all) ~62 bpm (ivab-angina) 70.6±10.1 bpm (placebo-alll)
Endpoint	Time To CV death or hospitalization for WHF	Time to CV death, hosp for AMI, hosp for new onset or WHF	Time to CV Death or non-fatal MI

6.1.2 Demographics

Randomized Set (RS)

A summary of the main baseline demographic data by FDA demonstrated no major discrepancies between treatment groups in the Randomized Set (RS), as see in the table below:

Table 30. Demographic characteristics of the RS

	Parameters	Ivabradine	Placebo
Age	Mean (SD)	60.7 (11.2)	60.1 (11.5)
Gender	Male (%) Female (%)	2462 (76.0) 779 (24.0)	2508 (76.8) 756 (23.2)
Ethnic	Caucasian (%) Asian (%) Black (%) Other (%)	2879 (88.8) 268 (8.3) 32 (1.0) 62 (1.9)	2892 (88.6) 264 (8.1) 43 (1.3) 54 (2.0)

Weight (kg)	Mean (SD)	80.9 (17.2)	80.7 (17.1)
Heart Rate (bpm)	Mean (SD)	79.7 (9.5)	80.1 (9.8)
Sitting SBP	Mean (SD)	122.0 (16.1)	121.4 (15.9)
Sitting DBP	Mean (SD)	75.7 (9.6)	75.6 (9.4)
Smoking Habits	Yes (%) Stopped (%) Never (%)	541 (16.7) 1355 (41.8) 1345 (41.5)	577 (17.7) 1364 (41.8) 1323 (40.5)

These FDA analyses matched exactly with their respective counterparts from the Sponsor's analysis of demographics in SHIFT (FSR Table (10.4.1.1)1, data not shown).

CHF-relevant demographic data of importance demonstrated that the SHIFT population did in fact suffer from important LV dysfunction, with a mean LVEF of 29%. About half of the enrolled patients were NYHA functional class II and about half were NYFC III. The class IV population was relatively small (1.7%), but evenly divided between the treatment groups. Per the protocol inclusion criteria, 98.8% of patients enrolled in SHIFT had been admitted to the hospital in the prior 12 months for worsening heart failure (WHF). Two-thirds of patients' CHF was ischemic in origin and one-third non-ischemic. The overall mean duration of the CHF diagnosis was 3.5 years. There were no relevant differences noted between the treatment groups in the RS with respect to CHF-relevant demographic factors, as shown in the following table (SHIFT FSR Table (10.4.1.2) 1 pg 90 / 4779):

Table 31. SHIFT CHF Characteristics at Baseline in the RS

			Ivabradine (N = 3241)	Placebo (N = 3264)	All (N = 6505)
Duration since CHF diagnosis (years)		n	3241	3264	6505
		Mean ± SD	3.5 ± 4.2	3.5 ± 4.2	3.5 ± 4.2
		Median	2.0	2.0	2.0
		Q1 ; Q3	0.6 ; 4.8	0.6 ; 4.9	0.6 ; 4.8
		Min ; Max	0.1 ; 40.7	0.0 ; 35.8	0.0 ; 40.7
Duration class (years)	< 2	n (%)	1621 (50.0)	1646 (50.4)	3267 (50.2)
	[2 ; 5[	n (%)	845 (26.1)	827 (25.3)	1672 (25.7)
	[5 ; 15[	n (%)	691 (21.3)	709 (21.7)	1400 (21.5)
	≥ 15	n (%)	84 (2.6)	82 (2.5)	166 (2.6)
Primary cause of CHF	Ischaemic	n (%)	2215 (68.3)	2203 (67.5)	4418 (67.9)
	Non-ischaemic	n (%)	1026 (31.7)	1061 (32.5)	2087 (32.1)
Main non-ischaemic reasons:	Idiopathic dilated cardiomyopathy	n (%)	664 (20.5)	685 (21.0)	1349 (20.7)
	Hypertensive	n (%)	226 (7.0)	253 (7.8)	479 (7.4)
	Valvular	n (%)	14 (0.4)	18 (0.6)	32 (0.5)
	Other	n (%)	122 (3.8)	105 (3.2)	227 (3.5)
Documented hospitalisation for worsening HF within the previous 12 months	No	n (%)	42# (1.3)	37 (1.1)	79 (1.2)
	Yes	n (%)	3199 (98.7)	3227 (98.9)	6426 (98.8)
NYHA class		n	3241	3264	6505
	Class I	n (%)	1 (0.03)	1 (0.03)	2 (0.03)
	Class II	n (%)	1585 (48.9)	1584 (48.5)	3169 (48.7)
	Class III	n (%)	1605 (49.5)	1618 (49.6)	3223 (49.5)
	Class IV	n (%)	50 (1.5)	61 (1.9)	111 (1.7)
LVEF (%)		n	3241	3264	6505
		Mean ± SD	29.0 ± 5.1	29.0 ± 5.2	29.0 ± 5.2
		Median	30.0	30.0	30.0
		Min ; Max	9 ; 39	7 ; 37	7 ; 39
	≤ 20%	n (%)	299 (9.2)	316 (9.7)	615 (9.5)
	]20 ; 25]	n (%)	513 (15.8)	482 (14.8)	995 (15.3)
	]25 ; 30]	n (%)	894 (27.6)	939 (28.8)	1833 (28.2)
	]30 ; 35]	n (%)	1533 (47.3)	1524 (46.7)	3057 (47.0)
	> 35	n (%)	2 (0.1)	3 (0.1)	5 (0.1)

 # excluding 1 patient with a deviation for undocumented hospitalisation for worsening HF within previous 12 months who was confirmed as having a hospitalisation by the investigator
N: Total number of patients in the considered treatment group; n: Number of patients concerned
% = (n/N) x 100 ; %' = (n/n') x 100
SD: Standard deviation

Other CV medical histories were similar between the placebo and ivabradine treatment groups in SHIFT (CAD, hypertension, MI, diabetes, AFib, AFlutter, and Renal failure). The largest between-group difference for CV preferred terms (PT) in the medical history was for "stroke" (7.0% in the ivabradine group versus 9.0% in the placebo group).

The SHIFT RS was well-treated pharmacologically, with

- 89.5% taking a beta-blocker

- 87.8% taking an ESC recommended beta-blocker or metoprolol tartrate
- 48.9% taking at least 50% of the ESC target daily BB dose
- 22.9% taking the full ESC target daily BB dose
- 91.1% taking an ACE inhibitor and/or an ARB
- 83.2% taking non-anti-aldosterone diuretics
- 60.3% taking an anti-aldosterone agent
- And 21.8% taking digitalis

Reviewer's note: approximately 22% of SHIFT patients were taking digoxin at baseline. Overall, 8.0% of the RS reported a prior medical history of AFib at baseline (SHIFT FSR Table (10.4.1.2) 2*).*

In a symptomatic HFrEF population with protocol-driven LVEFs ≤ 35% and a mean LVEF of 29%, baseline/background device therapy for CHF (ICD, CRT, CRT-D) was not well represented in SHIFT and did not / does not represent US guideline-driven medical practice in this population. Factors influencing device use at baseline in SHIFT may have included the regions in which SHIFT was conducted, as well as the rather restrictive exclusion criteria that were applied to those who did in fact have these devices (see SHIFT Exclusion Criteria, section 5.3.1.4 of this review). Device therapy at baseline in the RS is as follows:

Table 32. SHIFT Device Therapy for CHF at Baseline, RS

Implanted cardiac devices	Ivabradine (N = 3241)		Placebo (N = 3264)		All (N = 6505)	
	n	%	n	%	n	%
At least one device: pacemaker or CRT or ICD	**110**	**3.4**	**134**	**4.1**	**244**	**3.8**
Implantable Cardioverter Defibrillator	92	2.8	115	3.5	207	3.2
Device with pacemaker function	46	1.4	42	1.3	88	1.4
Conventional pacemaker only	8	0.3	5	0.2	13	0.2
Cardiac Resynchronisation Therapy	28	0.9	44	1.4	72	1.1
CRT and ICD	18	0.6	30	0.9	48	0.7

N: Total number of patients in the considered treatment group
n: Number of patients concerned
% = (n/N) x 100

Reviewer's comment: While ICD and CRT therapy were discouraged in SHIFT for the reasons noted above, they were explicitly excluded in both BEAUTIFUL (section 5.3.2.4 of this review) and SIGNIFY (section 5.3.3.4 of this review).

Randomized Set on 50% of ESC guideline directed Beta-Blocker Doses at Baseline (RS-BB-dose)

To assess the impact of baseline beta-blocker therapy dose on SHIFT outcomes, the sponsor identified a subset of patients who were taking at least 50% of the European Society of Cardiology (ESC) guideline-directed target daily doses of beta-blockers at baseline (the RS-BB-dose), defined for each of the predominantly used beta-blockers used in SHIFT as follows:

- Carvedilol: 25 mg/d
- Metoprolol succinate: 95 mg/d
- Bisoprolol: 5 mg/d
- Nebivolol: 5 mg/d
- Metoprolol tartrate: 75 mg/d

Reviewer's comment: Three beta-blockers are proven to reduce mortality and recommended for the treatment of HFrEF in the 2013 ACCF/AHA Heart Failure Guideline (Yancy CW et al. Circulation. 2013;128:1-163). The US guideline notes that the beta-blockers tested have not performed the same way in clinical trials:

> *"Three beta-blockers have been shown to be effective in reducing the risk of death in patients with chronic HFrEF: bisoprolol and sustained-release metoprolol (succinate), which selectively block beta-1–receptors; and carvedilol, which blocks alpha-1–, beta-1–, and beta-2–receptors. Positive findings with these 3 agents, however, should not be considered a beta-blocker class effect. Bucindolol lacked uniform effectiveness across different populations, and short-acting metoprolol tartrate was less effective in HF clinical trials.Beta-1 selective blocker nebivolol demonstrated a modest reduction in the primary endpoint of all-cause mortality or cardiovascular hospitalization but did not affect mortality alone in an elderly population that included patients with HFpEF (472)… Clinicians should make every effort to achieve the target doses of the beta-blockers shown to be effective in major clinical trials."*

According this the US guideline, 50% of the mean doses achieved in clinical trials for the three recommended beta-blockers for chronic HF patients are as follows:

- *Carvedilol: 18.5 mg/d*
- *Metoprolol succinate (CR/XL): 79.5 mg/d*
- *Bisoprolol: 4.3 mg/d.*

Therefore, the definition of RS-BB-dose with respect the approved beta-blockers for this indication in the US is accurate, in that the anyone meeting the 50% of

ESC-guideline target dose cutoffs for these three drugs will also meet the 50% of US guideline targeted doses for them as well.

Overall demographics in the RS-BB-dose

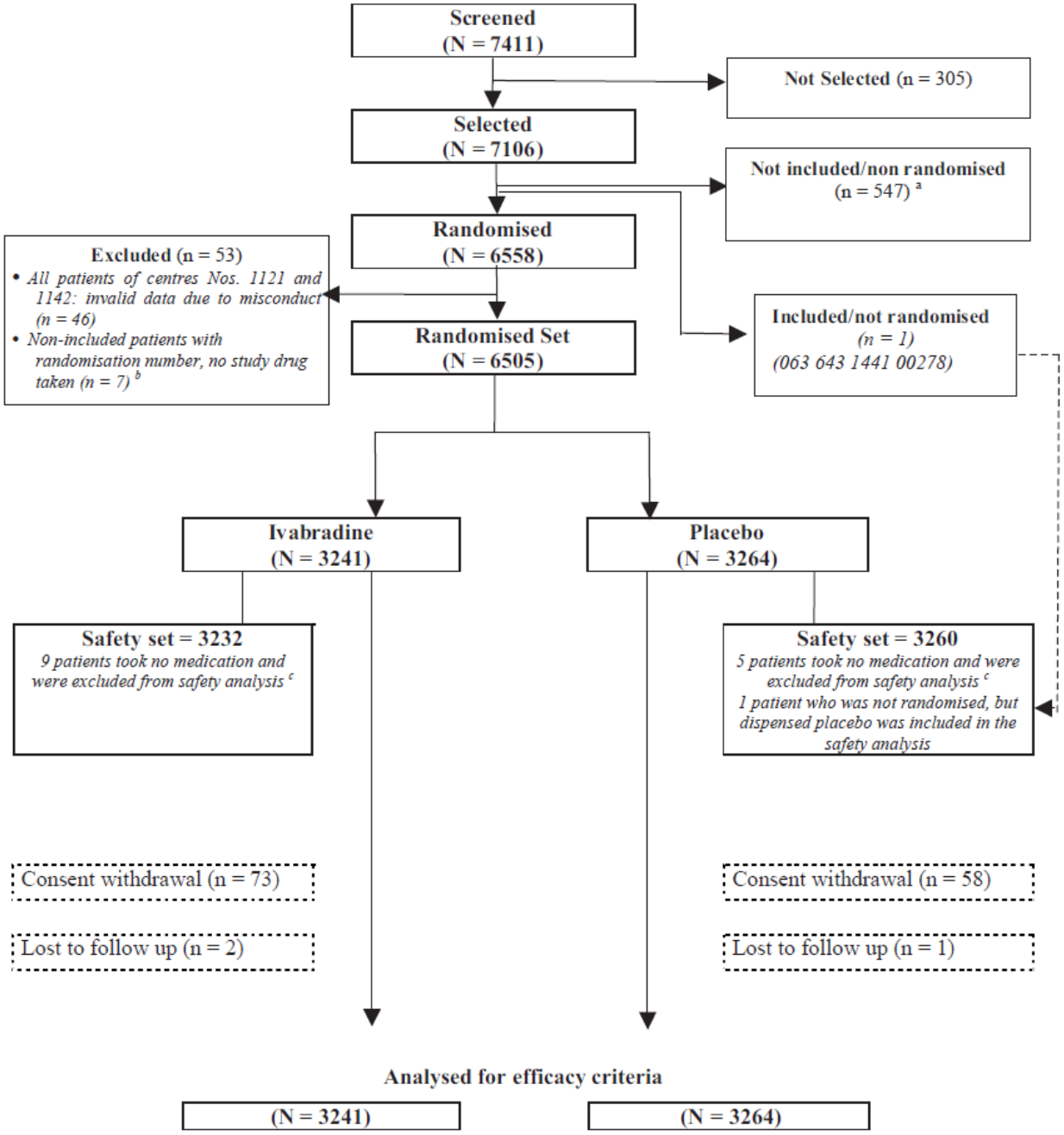
Other than for weight and Ethnic origin, the demographics for the RS-BB-dose were similar to those described for the RS (subjects in the RS-BB-dose were on average 4 kg heavier than subjects in the RS and more likely to be Caucasian (93.6% versus 88.7% in the RS)). There are no relevant differences noted between the groups in the RS-BB-dose. Specifically, the overall RS-BB-dose demonstrated the following:

- Mean LVEF 29%
- Approximately half NYHA class II and approximately half NYHA class III with only 1.1% NYHA class IV
- 69.3% of HFrEF ischemic in origin
- The most common etiology of non-ischemic HFrEF was idiopathic dilated cardiomyopathy (19.1%)
- Mean duration of HFrEF was 3.7 years.

6.1.3 Subject Disposition

The disposition of SHIFT patients through the trial are demonstrated in the figure below (SHIFT FSR p 78/4779):

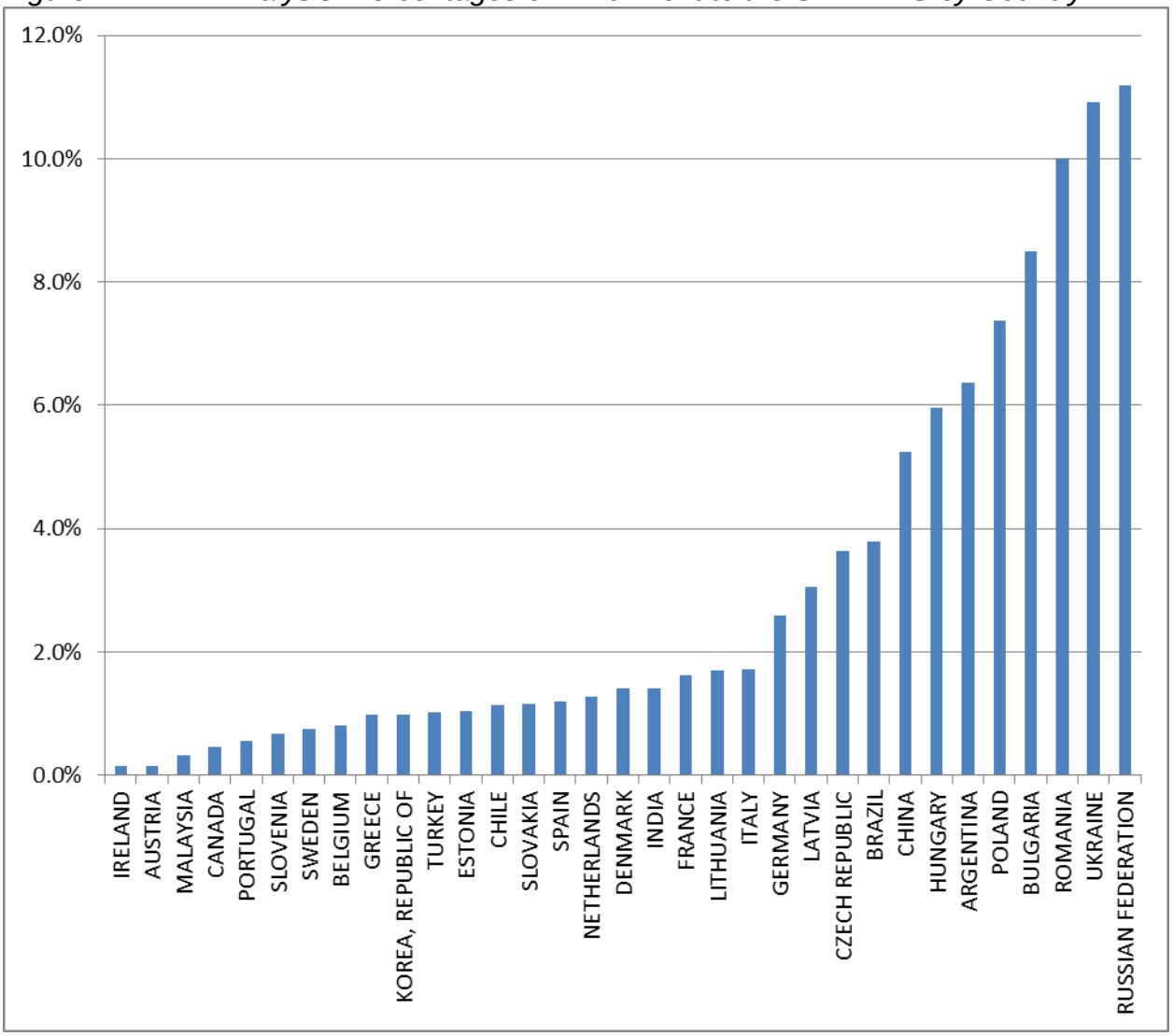
Figure 20. Disposition of Subjects in SHIFT



There were 6558 subjects randomized into the SHIFT trial. The mean duration of follow-up was 22.0 months. The Applicant defined the "Randomized Set" as all subjects with a randomization number allocated by the interactive response system who were dispensed study drug. Note that this is more a "pre protocol" or "treated" population. Forty-six subjects constituting the total enrollment of 2 Polish study centers, were excluded from the

Randomized Set for concerns over invalid data due to study center misconduct (GCP violations), and 7 subjects who did not meet inclusion criteria and never received study drug were also excluded. The exclusion of these subjects was determined prior to unblinding to avoid introducing bias. A sensitivity analysis was performed by the sponsor and by FDA in which subjects from the study centers were not excluded – results were consistent with the main analysis. Excluding the 46 patients from the Polish centers and the 7 patients that never received study drug removed a total of 53 subjects, leaving a total of 6505 patients as the "Randomized Set" (RS) that the sponsor and FDA subsequently used for performing efficacy analyses. The enrollment by country in the figure below reflects the fact that SHIFT was conducted totally outside the US, primarily in Eastern Europe:

Figure 21. FDA Analysis: Percentages of Enrollment to the SHIFT RS by Country



The FDA analysis of the disposition of patients in the RS is as follows:

Table 33. FDA SHIFT Analysis: Disposition of Subjects by Treatment Group, RS

Status	**Ivabradine (N=3241)**	**Placebo (N=3264)**	**Total (N=6505)**
	n (%)	n (%)	n (%)
Consent Withdrawal	73 (2.3)	58 (1.8)	131 (2.0)
Death	503 (15.5)	553 (16.9)	1056 (16.2)
Lost to Follow-up	2 (<0.1)	1 (<0.1)	3 (<0.1)
Study Completed	2663 (82.2)	2652 (81.3)	5315 (81.7)

The FDA disposition of patients in the overall RS matched the sponsor disposition exactly, as can be seen by comparing the FDA table above to the sponsor's disposition table below (from the SHIFT FSR 5/4779):

Table 34. Applicant SHIFT Analysis: Disposition of Subjects by Treatment, RS

		Ivabradine	**Placebo**	**All**
Included and randomised (RS)	**N**	**3241**	**3264**	**6505**
Died before completion	n (%)	503 (15.5)	553 (16.9)	1056 (16.2)
Consent withdrawal	n (%)	73 (2.3)	58 (1.8)	131 (2.0)
Lost to follow-up	n (%)	2 (< 0.1)	1 (< 0.1)	3 (< 0.1)
Completed	n (%)	2663 (82.2)	2652 (81.3)	5315 (81.7)
Patients analysed	n (%)	**3241 (100.0)**	**3264 (100.0)**	**6505 (100.0)**
RS_{BBdose}	n (%)	**1581 (48.8)**	**1600 (49.0)**	**3181 (48.9)**
Safety Set	n (%)	**3232 (99.7)**	**3260 (99.9)**	**6492 (99.8)**

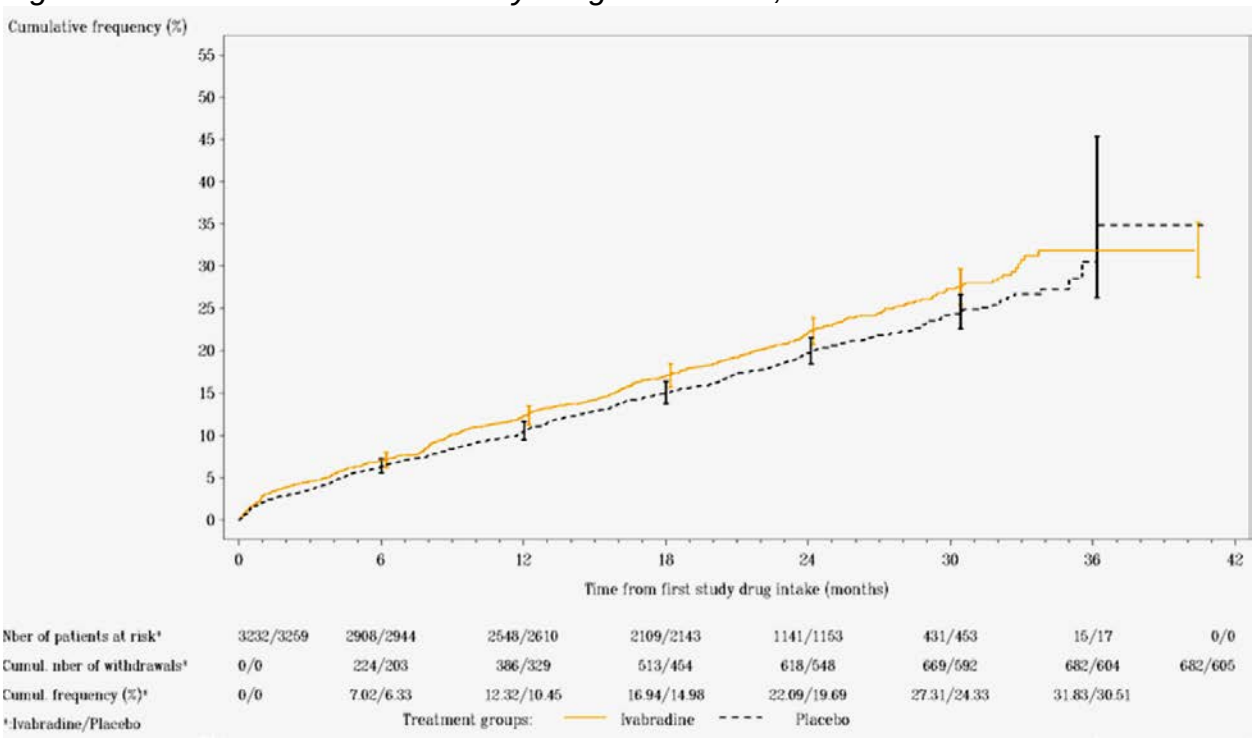
N: Total number of patients in the randomised treatment group
n: Number of patients concerned
% = (n / N) x 100

Reviewer's comment: The Safety Set (SS) was defined as all patients having received at least one dose of study drug. The SS was smaller than the RS by a total of 13 patients because:

- *9 in the ivabradine group and 5 in the placebo group were excluded from the SS because they never took any study medication.*
- *One patient who received study drug (placebo) without being randomized was included in the SS in the placebo group.*

Overall, 1287 subjects (19.8% of the RS) prematurely discontinued study treatment: 632(21.0%) subjects in the ivabradine treatment arm and 605 (18.5%) of patients in the placebo arm. The applicant's Kaplan-Meier analysis of the occurrence of these events is as follows (SHIFT FSR p 81/4779):

Figure 22. Time to Permanent Study Drug Withdrawal, RS



The premature withdrawals were mainly due to adverse events in both treatment arms, though overall cardiac disorders occurred less frequently in the ivabradine treatment arm, a difference in favor of ivabradine therapy that was somewhat driven by fewer heart failure adverse events in the active treatment group, per the table below (SHIFT FSR p 82/4779):

Figure 23. Reasons Reported for Permanent Study Drug Withdrawal (in 10 or more subjects in the ivabradine group), RS

		Ivabradine (N = 3241)	Placebo (N = 3264)	All (N = 6505)
Total number of patients withdrawn:		**n = 682**	**n = 605**	**n = 1287**
HR < 50 bpm at the 2.5 mg b.i.d. dose without symptoms of bradycardia	**n (%)**	**23 (3.4)**	**3 (0.5)**	**26 (2.0)**
Adverse events* All	**n (%)**	**443 (65.0)**	**380 (62.8)**	**823 (64.0)**
Cardiac disorders	**n (%')**	**283 (63.9)**	**249 (65.5)**	**532 (64.6)**
+Cardiac arrhythmias	n (%')	205 (46.3)	163 (42.9)	368 (44.7)
Atrial fibrillation	n (%')	133 (30.0)	112 (29.5)	245 (29.8)
Atrial flutter	n (%')	13 (2.9)	8 (2.1)	21 (2.6)
Bradycardia	n (%')	20 (4.5)	5 (1.3)	25 (3.0)
+Heart failures	n (%')	62 (14.0)	67 (17.6)	129 (15.7)
Cardiac failure	n (%')	56 (12.6)	65 (17.1)	121 (14.7)
Nervous system disorders	**n (%')**	**26 (5.9)**	**33 (8.7)**	**59 (7.2)**
Ischaemic stroke	n (%')	10 (2.3)	11 (2.9)	21 (2.6)
Investigations	**n (%')**	**33 (7.5)**	**11 (2.9)**	**44 (5.4)**
Heart rate decreased	n (%')	27 (6.1)	5 (1.3)	32 (3.9)
Gastrointestinal disorders	**n (%')**	**20 (4.5)**	**15 (4.0)**	**35 (4.3)**
Eye disorders	**n (%')**	**10 (2.3)**	**6 (1.6)**	**16 (1.9)**
Surgical and medical procedures	**n (%')**	**10 (2.3)**	**6 (1.6)**	**16 (1.9)**
Concomitant treatment	**n (%)**	**18 (2.6)**	**21 (3.5)**	**39 (3.0)**
Antiarrhythmics, class III	n (%')	15 (83.3)	13 (61.9)	28 (71.8)
Non medical reason	**n (%)**	**198 (29.0)**	**201 (33.2)**	**399 (31.0)**

** Adverse events by SOC: System organ class; +HLGT: High level group term; PT: Preferred term*
N: Total number of patients in the considered treatment group
n: number of patients with reason or reason grouping (category)
% = (n/total number of patients withdrawn × 100
%' = (n/number of patients in category) x 100

However, symptomatic bradycardia and asymptomatic heart rate decreases were, as expected, more common in the Ivabradine treatment group. Furthermore, while the occurrence of AFib and AFlutter do not appear to be very different in this analysis of reason for premature withdrawal, among the adverse events that led to withdrawal from study drug, AFib/AFlutter was the leading cause (4.2%, 2.5%PY *versus* 3.5%, 2.1%PY, for ivabradine vs placebo respectively), an outcome that it should be kept in mind was protocol driven (loss of sinus rhythm mandating study withdrawal). AFib was also one of the most frequent EAEs leading to a surgical or medical procedure (1.3%, 0.8%PY versus 0.7%, 0.4%PY, ivabradine vs placebo respectively). A small excess in withdrawal due to class III antiarrhythmic use, possibly due to the occurrence of AFib, is also seen in the table above.

Reviewer's comment: An impressive achievement - to not know the vital status of only 3 subjects in a multinational study during which 1056 / 6505 (16%) of the study population died in addition to which 20% of the RS withdrew prematurely to due adverse events.

6.1.4 Analysis of Primary Endpoint(s)

The primary composite endpoint (PCE) of SHIFT was the first event among cardiovascular death (including death of unknown cause) or hospitalization for worsening heart failure, analyzed and reported by the applicant as follows:

- For the ITT analysis of the RS, the superiority of ivabradine over placebo in the reduction of the incidence of the primary endpoint was demonstrated, using a Cox proportional hazards model adjusted for beta-blocker intake at randomization, with an estimate of the hazard ratio of 0.82 (95% CI [0.75; 0.90], p < 0.0001). This outcome was driven by hospitalizations for WHF, though a non-significant positive lean in the CV death component of the PCE contributed to the overall outcome.

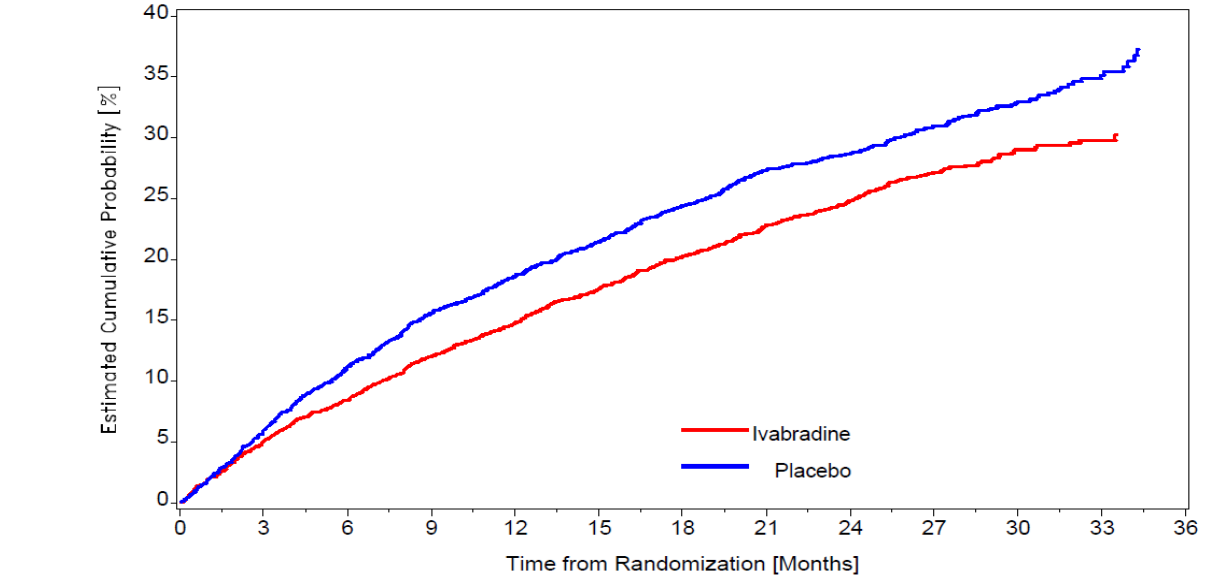
- For the ITT analysis of the RS-BB-dose, the estimate of the hazard ratio of the primary endpoint in this analysis set was 0.90 (95% CI [0.77; 1.04]), indicating a 10% RRR, but statistical significance was not reached (p = 0.155).

The FDA-generated results of the primary composite efficacy endpoint and its components are shown in the table below, followed by the Kaplan-Meier Plot of the results for the RS:

Table 35. FDA SHIFT Analysis: SHIFT Primary Composite Endpoint, RS and RS-BB-dose

Analysis Sets	Ivabradine		Placebo		HR (95% CI)	p-value
	n/N	%	n/N	%		
RS						
PCE	793/3241	24.5	937/3264	28.7	0.82 (0.75, 0.90)	<0.0001
CV Death	449/3241	13.9	491/3264	15.0	0.91 (0.80, 1.03)	0.128
Hospitalization for WHF	514/3241	15.9	672/3264	20.6	0.74 (0.66, 0.83)	<0.0001
RS-BB-dose						
PCE	330/1581	20.9	362/1600	22.6	0.90 (0.77, 1.04)	0.155

Figure 24. FDA SHIFT Analysis: Kaplan-Meier Plot - Primary Composite Endpoint



No. at risk													
Ivabradine	3241	3053	2932	2792	2613	2434	2199	1783	1290	832	477	182	39
Placebo	3264	3053	2870	2702	2505	2312	2077	1676	1178	787	462	204	35

Point estimates for the treatment effect favored ivabradine in all predefined subgroups, though the upper limits of the 95% CI exceeded unity for Age $\geq$ 65 and Baseline Heart Rate below the median of 77 bpm. There was a positive interaction p-value for the HR below 77 bpm, as seen in the following table (SHIFT FSR 114/4779):

Table 36. Primary Composite Endpoint for Subgroups of the RS

	Ivabradine		Placebo		Hazard ratio	Interaction
	% (n/N)	%PY	% (n/N)	%PY	E [95% CI]	p-value
Age						
< 65 years	20.6 (407/1976)	11.8	25.6 (527/2055)	15.6	0.76 [0.67 ; 0.87]	-
≥ 65 years	30.5 (386/1265)	19.0	33.9 (410/1209)	21.3	0.89 [0.77 ; 1.02]	0.099
Gender						
Men	25.4 (624/2462)	15.1	28.9 (725/2508)	17.8	0.84 [0.76 ; 0.94]	-
Women	21.7 (169/779)	12.6	28.0 (212/756)	17.3	0.74 [0.60 ; 0.91]	0.260
Beta-blocker intake at randomisation						
No	29.4 (101/344)	18.1	39.3 (134/341)	27.3	0.68 [0.52 ; 0.88]	-
Yes	23.9 (692/2897)	14.1	27.5 (803/2923)	16.7	0.85 [0.76 ; 0.94]	0.103
Aetiology of HF						
Non-ischaemic	21.3 (218/1026)	12.7	27.9 (296/1061)	17.8	0.72 [0.60 ; 0.85]	-
Ischaemic	26.0 (575/2215)	15.3	29.1 (641/2203)	17.6	0.87 [0.78 ; 0.97]	0.060
NYHA class at baseline						
Class II	18.9 (300/1585)	10.7	22.5 (356/1584)	13.2	0.81 [0.69 ; 0.94]	-
Class III or IV	29.8 (493/1655)	18.4	34.5 (580/1679)	22.3	0.83 [0.74 ; 0.94]	0.793
History of diabetes						
No	23.2 (525/2268)	13.6	27.1 (611/2258)	16.5	0.83 [0.74 ; 0.93]	-
Yes	27.5 (268/973)	16.6	32.4 (326/1006)	20.5	0.81 [0.69 ; 0.95]	0.861
History of hypertension						
No	25.4 (274/1079)	15.4	29.7 (330/1112)	19.2	0.81 [0.69 ; 0.95]	-
Yes	24.0 (519/2162)	14.0	28.2 (607/2152)	17.0	0.83 [0.74 ; 0.93]	0.779
Heart rate at baseline*						
< 77 bpm	21.4 (339/1583)	12.3	22.8 (356/1561)	13.2	0.93 [0.80 ; 1.08]	-
≥ 77 bpm	27.4 (454/1657)	16.8	34.2 (581/1700)	22.3	0.75 [0.67 ; 0.85]	**0.0288**

Of note, the slight imbalance in patients who withdrew consent (73 in the ivabradine arm and 58 in the placebo arm, for a total of 131 subjects) did not impact the overall efficacy result – regardless of whether these subjects were completely removed from the analysis or all were re-classified as having experienced primary endpoint events, the primary endpoint analysis was unchanged.

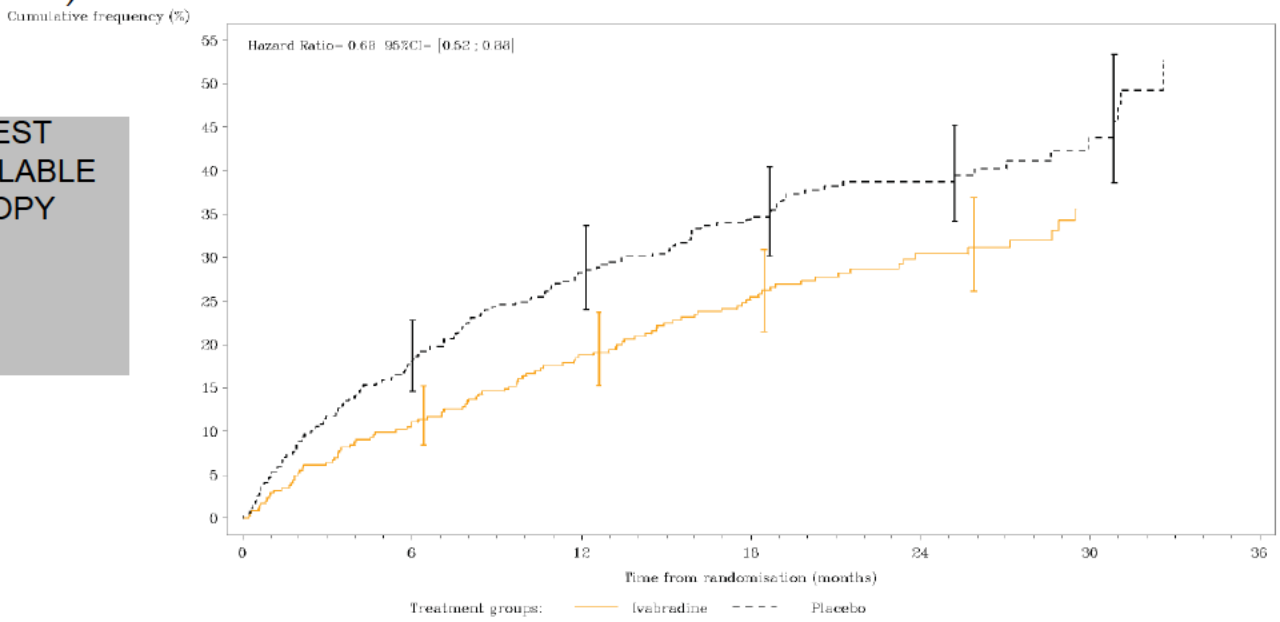
FDA's analysis of the primary endpoint for both the RS and the RS-BB-dose were in exact agreement with the SHIFT results as reported in the submitted SHIFT FSR. The applicant also notes that, *The sensitivity analysis (without adjustment) and the prognostic factor analysis (with adjustment on beta-blocker intake at randomization, NYHA class, LVEF, etiology of CHF (ischemic or not), age, systolic blood pressure, heart rate and estimated glomerular filtration rate, at baseline) confirmed these results: hazard ratio = 0.82 [0.75 ; 0.90] for the unadjusted analysis and hazard ratio = 0.83 [0.75 ; 0.91] for the analysis adjusted on prognostic factors.*

FDA Reviewer's Comments:

- *The biometrics reviewer had some concern that the increase in the trial sample size and number of primary events from Amendments 5 and 6 may have inadvertently resulted in an inflation of the Type I error probability if these adjustments were influenced by internal trial data. To address this concern, the FDA biometrics reviewer performed an analysis to adjust p-value using the valid statistical test method of Cui, Hung, and Wang (1999, Biometrics). The results of this cross-check support the sponsor's unweighted sensitivity test.*

- *Efficacy for the RS-BB-dose group leans toward a lesser benefit for the PCE compared to the overall RS which contains patients on lesser doses of beta-blockers, or no beta-blockers at all. To shed more light on the role that background beta-blockers play in the overall efficacy of ivabradine for the PCE, note the following three K-M plots showing progressively decreasing efficacy with progressively increasing doses of background beta-blockers, going from the RS-subgroup on no beta-blockers at randomization (*Figure 25*), to the RS-subgroup on any dose of beta-blockers at randomization (*Figure 26*), to the RS-BB-dose subset taking at least 50% of ESC targeted doses of the beta-blockers that were used in SHIFT at randomization (*Figure 27*):*

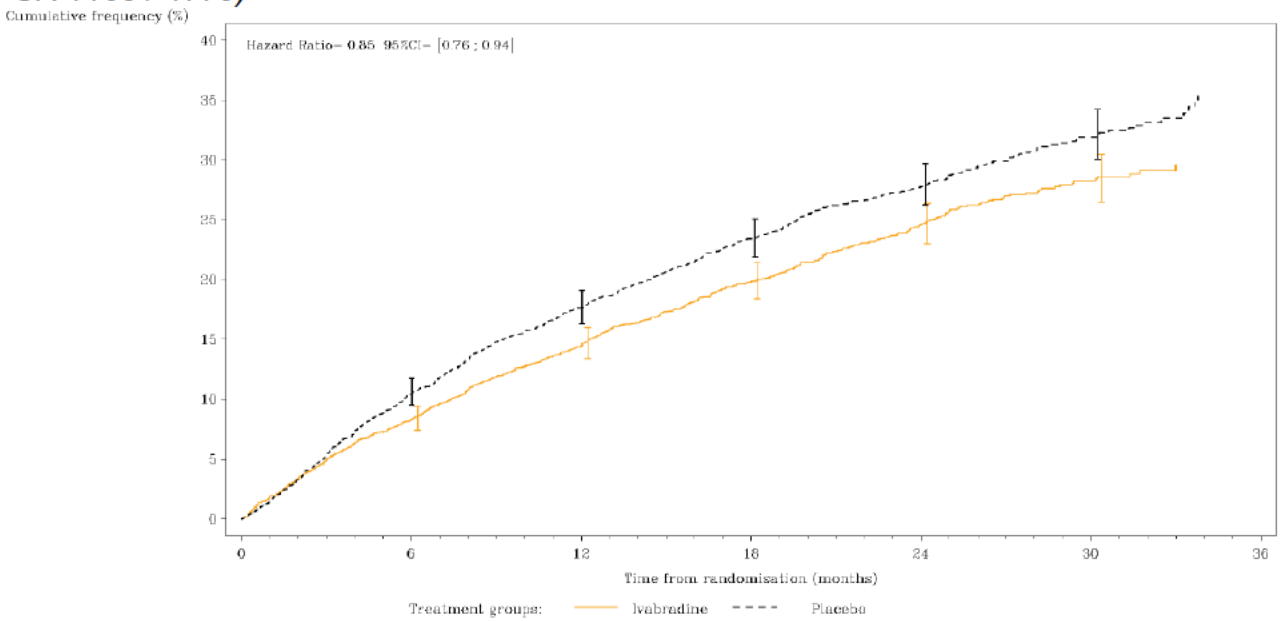
Figure 25. PCE - KM curves - No Beta-Blocker at Randomization, RS (SHIFT FSR 1102 / 4779)



Nber of patients at risk*	344/341	304/275	268/233	211/186	114/90	45/36	3/3
Cumul. nber of endpoints*	0/0	38/61	64/95	85/115	96/125	101/130	101/134
Cumul. frequency (%)*	0/0	11.1/18.01	18.79/28.26	25.51/34.71	30.45/38.72	35.53/43.87	35.53/52.68

*Ivabradine/Placebo

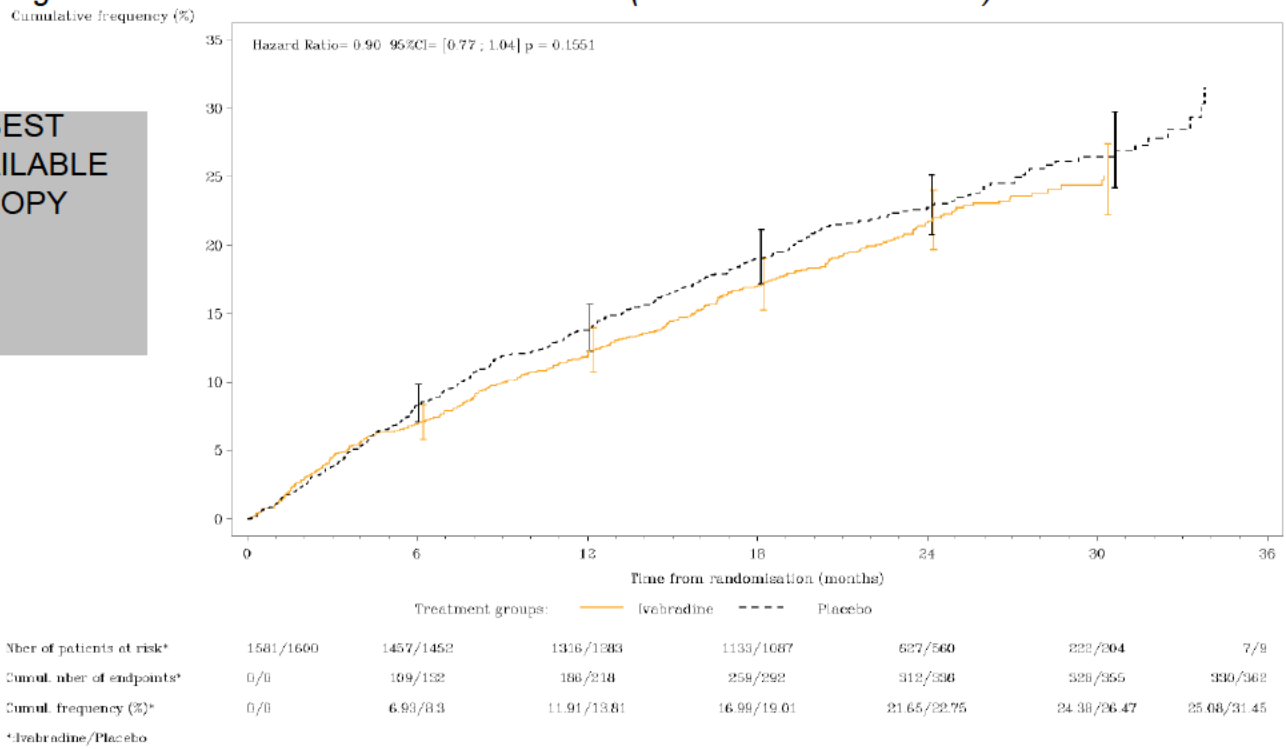
Figure 26. PCE - KM curves - Any Dose of Beta-Blocker at Randomization, RS (SHIFT FSR 1103 / 4779)



Nber of patients at risk*	2897/2923	2624/2593	2332/2356	1962/1875	1077/999	402/403	14/14
Cumul. nber of endpoints*	0/0	358/305	413/509	553/660	649/751	687/792	692/803
Cumul. frequency (%)*	0/0	8.27/10.48	14.47/17.63	19.81/23.4	24.54/27.77	28.33/31.9	29.61/35.5

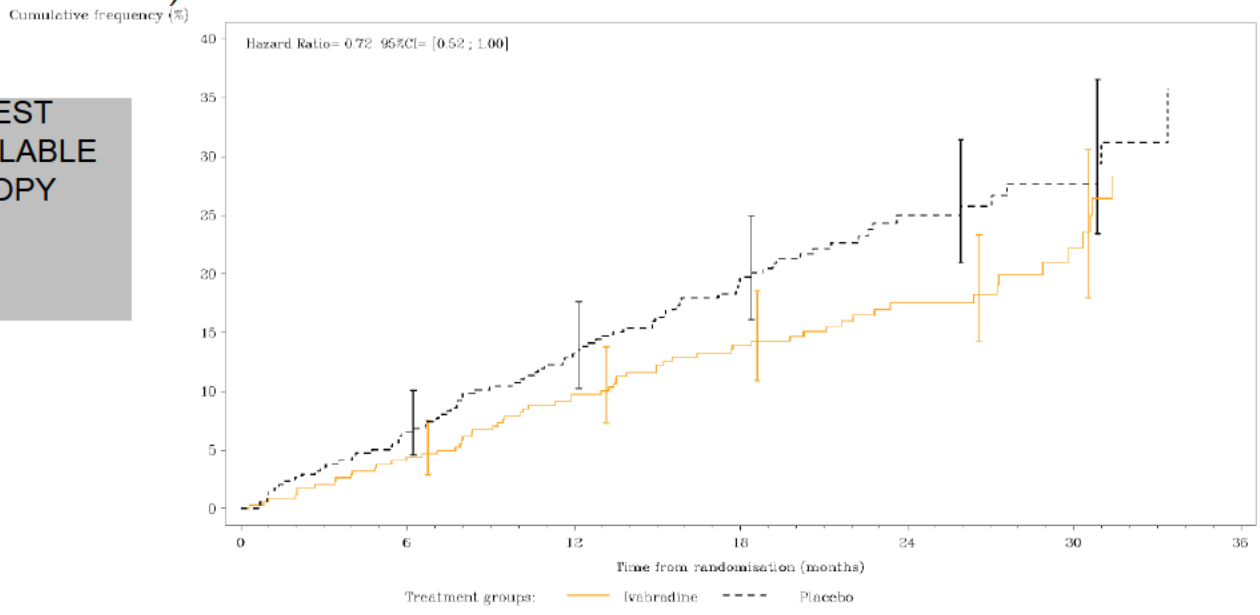
*Ivabradine/Placebo

Figure 27. PCE - KM curves - RS-BB-dose (SHIFT FSR 1166 / 4779)



- *The same trend is apparent for the CV Death component of the PCE, with decreasing benefit in the reduction of CV Death noted for the same three subgroups with progressively higher background doses of beta-blockers, going from the KM curves for CV Death in the RS-subgroup on no beta-blockers at randomization (*Figure 28*), to the KM curves for CV Death in the RS-subgroup on any dose of beta-blockers at randomization (*Figure 29*), to the KM curves for CV Death in the RS-BB-dose subset taking at least 50% of ESC targeted doses of the beta-blockers that were used in SHIFT at randomization (*Figure 30*):*

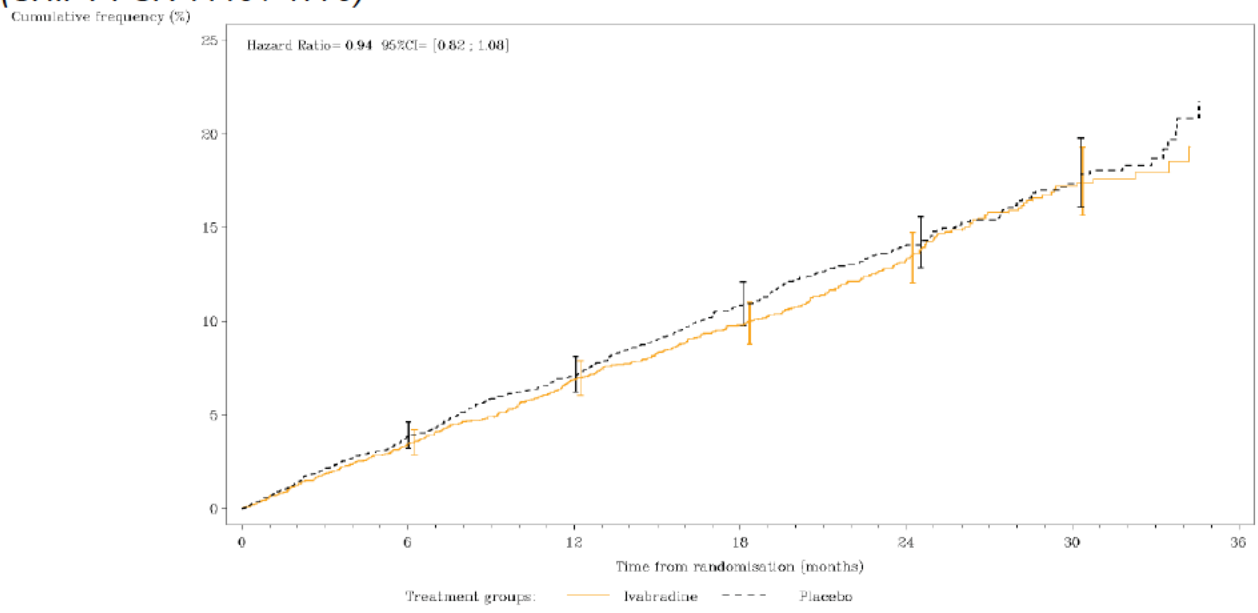
Figure 28. CV Death - KM curves - No Beta-Blocker at Randomization, RS (SHIFT FSR 1118 / 4779)



Nber of patients at risk*	344/341	327/312	295/281	248/225	143/111	60/48	3/5
Cumul. nber of endpoints*	0/0	15/22	33/44	46/64	54/75	59/78	63/81
Cumul. frequency (%)*	0/0	4.38/6.51	9.73/13.17	13.9/19.71	17.53/24.97	22.21/27.63	28.16/35.75

*Ivabradine/Placebo

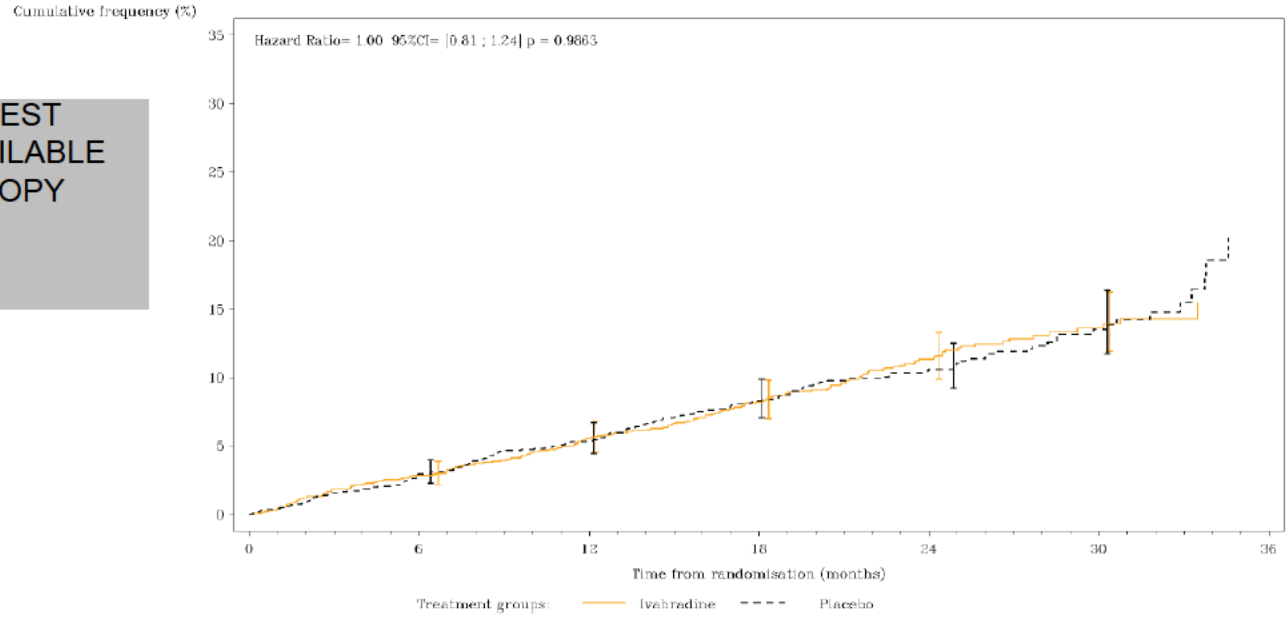
Figure 29. CV Death - KM curves - Any dose of Beta-Blocker at Randomization, RS (SHIFT FSR 1119 / 4779)



Nber of patients at risk*	2897/2923	2758/2782	2523/2536	2185/2166	1234/1207	471/466	19/15
Cumul. nber of endpoints*	0/0	99/111	195/204	271/302	340/368	380/399	385/410
Cumul. frequency (%)*	0/0	3.45/3.82	6.87/7.08	9.8/10.84	13.38/14.09	17.22/17.33	19.31/21.7

*Ivabradine/Placebo

Figure 30. CV Death - KM curves - RS-BB-dose (SHIFT FSR 1167 / 4779)



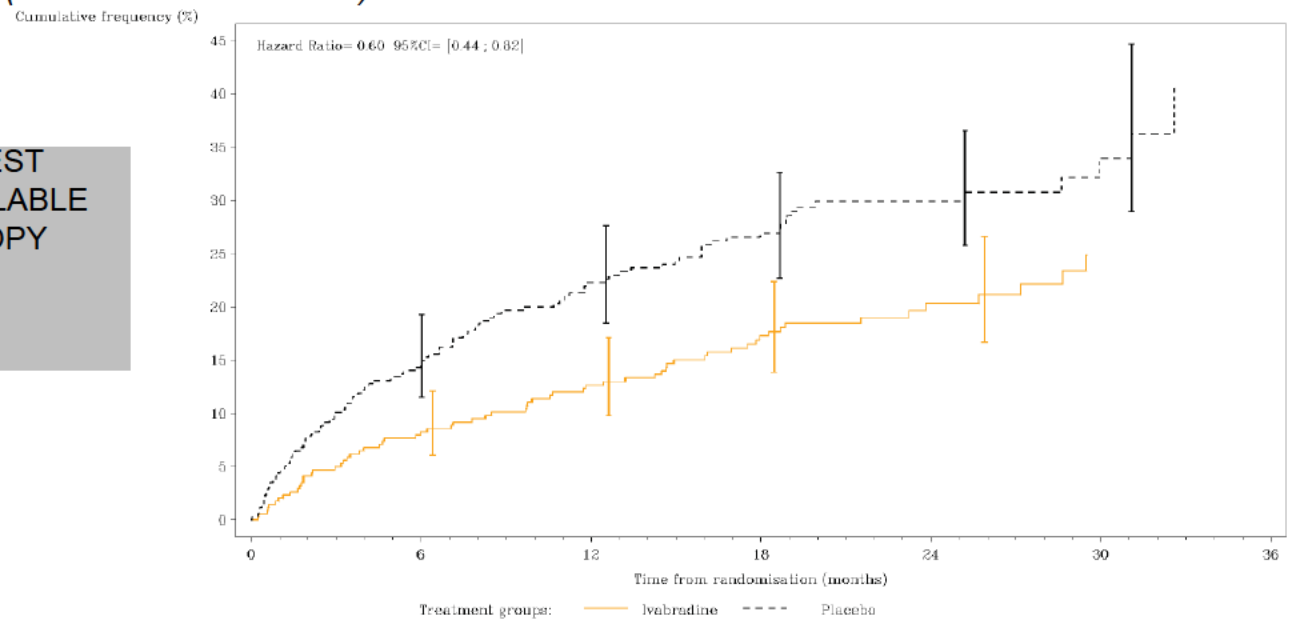
Nber of patients at risk*	1581/1600	1520/1535	1407/1404	1242/1227	711/666	257/243	16/9
Cumul. nber of endpoints*	0/0	45/47	86/85	124/126	160/153	173/167	176/175
Cumul. frequency (%)*	0/0	2.86/2.96	5.53/5.39	8.21/8.28	11.33/10.6	13.6/13.5	15.44/20.2

*Ivabradine/Placebo

Likewise, a similar trend is apparent for the Hospitalization for WHF component of the PC, with decreasing benefit in the reduction of hospitalization for WHF noted for the same three sub-groups with progressively higher background doses of beta-blockers, going from the KM curves for hospitalization for WHF in the RS-subgroup on no beta-blockers at randomization (

- Figure 31*), to the KM curves for hospitalization for WHF in the RS-subgroup on any dose of beta-blockers at randomization (*Figure 32*), to the KM curves for hospitalization for WHF in the RS-BB-dose subset taking at least 50% of ESC targeted doses of the beta-blockers that were used in SHIFT at randomization (*Figure 33*):*

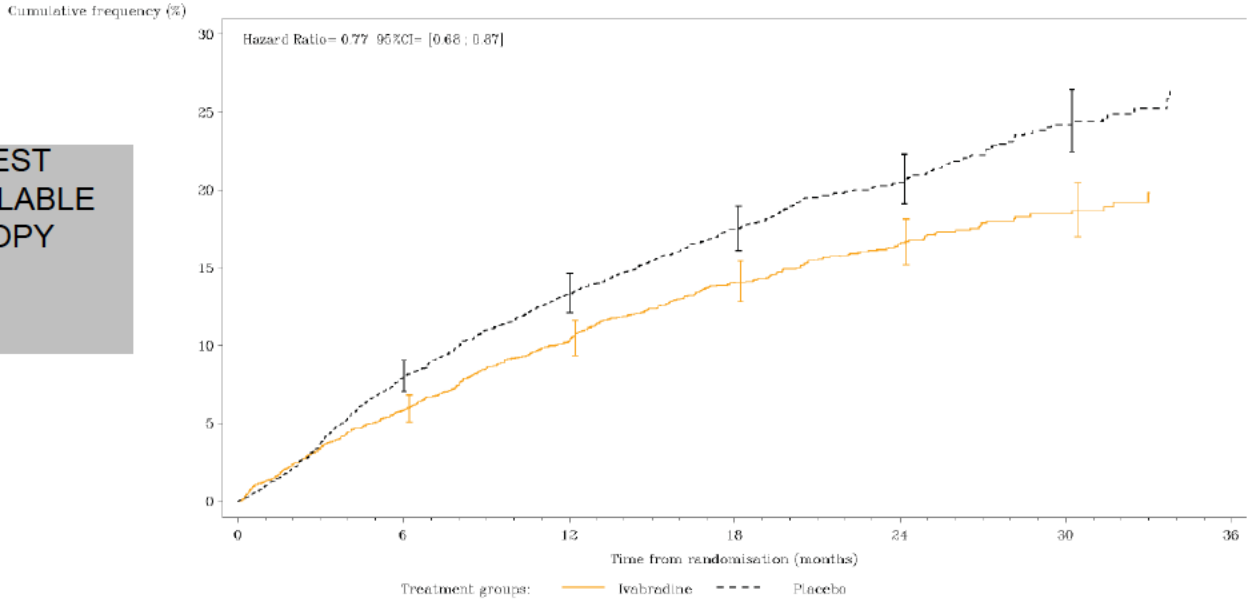
Figure 31. Hospitalization for WHF - KM curves - No Beta-Blocker at Randomization, RS (SHIFT FSR 1134 / 4779)



Nber of patients at risk*	344/341	304/275	268/233	211/186	114/90	45/36	2/3
Cumul. nber of endpoints*	0/0	28/49	42/73	55/86	61/93	65/96	65/98
Cumul. frequency (%)*	0/0	8.29/14.65	12.66/22.31	17.27/26.93	20.35/29.91	24.87/33.97	24.87/40.5

*Ivabradine/Placebo

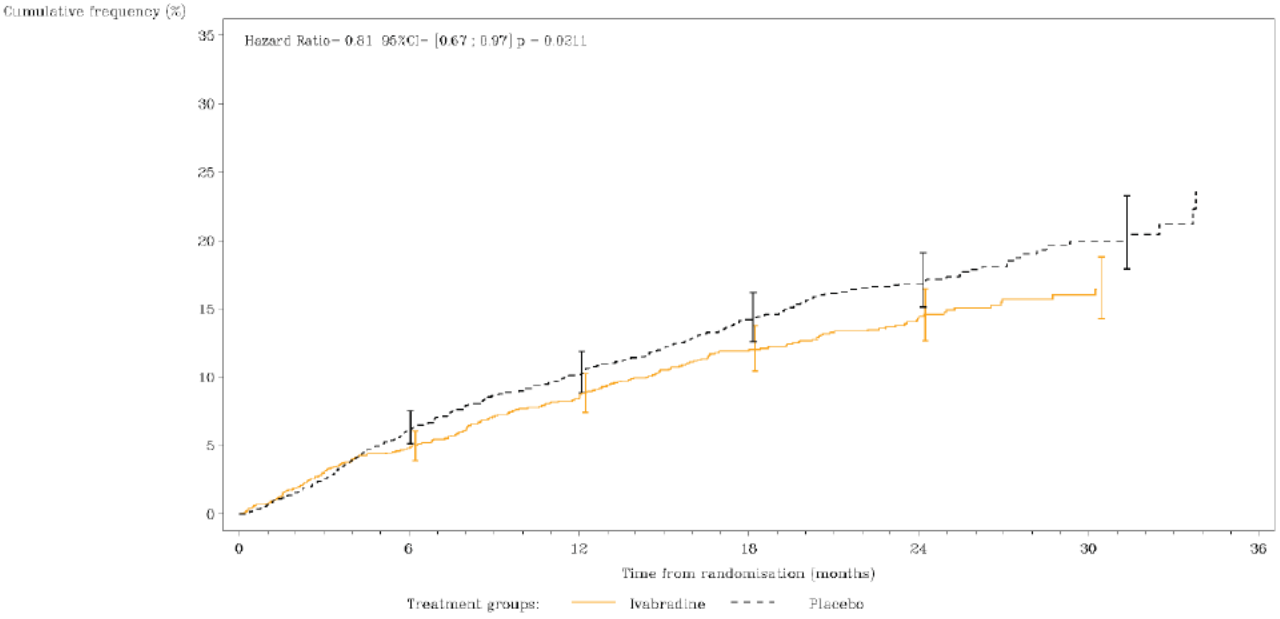
Figure 32. Hospitalization for WHF - KM curves - Any beta-blocker Dose at Randomization, RS (SHIFT FSR 1135 / 4779)



Nber of patients at risk*	2897/2923	2624/2593	2332/2256	1962/1875	1077/999	402/403	14/14
Cumul. nber of endpoints*	0/0	165/227	287/374	380/476	427/535	445/568	449/574
Cumul. frequency (%)*	0/0	5.81/7.93	10.29/13.3	14.03/17.45	16.53/20.49	18.46/24.2	19.83/26.51

*:Ivabradine/Placebo

Figure 33. Hospitalization for WHF - KM curves - RB-BB-dose (SHIFT FSR 1168 / 4779)



Nber of patients at risk*	1581/1600	1457/1452	1316/1283	1133/1087	627/560	222/204	7/9
Cumul. nber of endpoints*	0/0	75/97	130/158	178/212	203/242	212/256	213/260
Cumul. frequency (%)*	0/0	4.82/6.18	8.48/10.22	11.95/14.22	14.32/16.88	16.03/19.96	16.41/23.52

*:Ivabradine/Placebo

6.1.5 Analysis of Secondary Endpoints(s)

Adjudicated Death (See also Section 6.1.7, Subpopulations, Heart Rate at Baseline)

There were a total of 1055 adjudicated deaths in from the RS of SHIFT.[5] There were fewer deaths overall in the ivabradine treatment group, as well as fewer CV deaths, deaths from heart failure, and non-cardiovascular deaths. On note, there more sudden cardiac deaths (adjudicated as arrhythmic deaths) in the ivabradine group as compared to the placebo group. Causes of adjudicated deaths from the RS are shown in the following table:

Table 37. FDA SHIFT Analysis: Causes of Deaths by Treatment Group, RS

	Ivabradine (N=3241)		Placebo (N=3264)	
	n	%	n	%
Death from any cause	503	15.5	552	16.9
Cardiovascular death	449	13.9	491	15.0
Sudden cardiac death	232	7.2	220	6.7
Death from heart failure	113	3.5	151	4.6
Non-cardiovascular death	54	1.7	61	1.9

Estimates of the treatment effect of ivabradine on these different causes of death in the RS are presented in the following table:

[5] The applicant reports 1055 death in the RS. This differs by 19 deaths from the 1074 reported in the SS because 21 subjects died after their last visit date (9 ivabradine, 12 placebo), one patient (placebo) was included in the study but never randomized, and 3 patients who died were included in the RS who never took study drug (2 ivabradine, 1 placebo).

Table 38. FDA SHIFT Analysis: Estimates of Treatment Effect on Causes of Death, RS

	Hazard Ratio (95% CI)	p-value
Death from any cause	0.90 (0.80, 1.02)	0.092
Cardiovascular death	0.91 (0.80, 1.03)	0.128
Sudden cardiac death	1.05 (0.87, 1.26)	0.630
Death from heart failure	0.74 (0.58, 0.94)	0.014
Non-cardiovascular death	0.87 (0.60, 1.25)	0.455

The point estimates of the treatment effect of ivabradine on all predefined subgroups favored ivabradine for all-cause mortality, CV death, and Death from HF except again for the subgroup with baseline heart rates <77 bpm, which demonstrated a point estimate for ivabradine treatment effect that exceeded unity for all three death categories, as seen in the following three forests plots for ACM, Death-CV, and Death-HF, respectively:

Figure 34. Forest Plot - Estimate of Treatment Effect on Death from Any Cause, Pre-defined Subgroups, RS

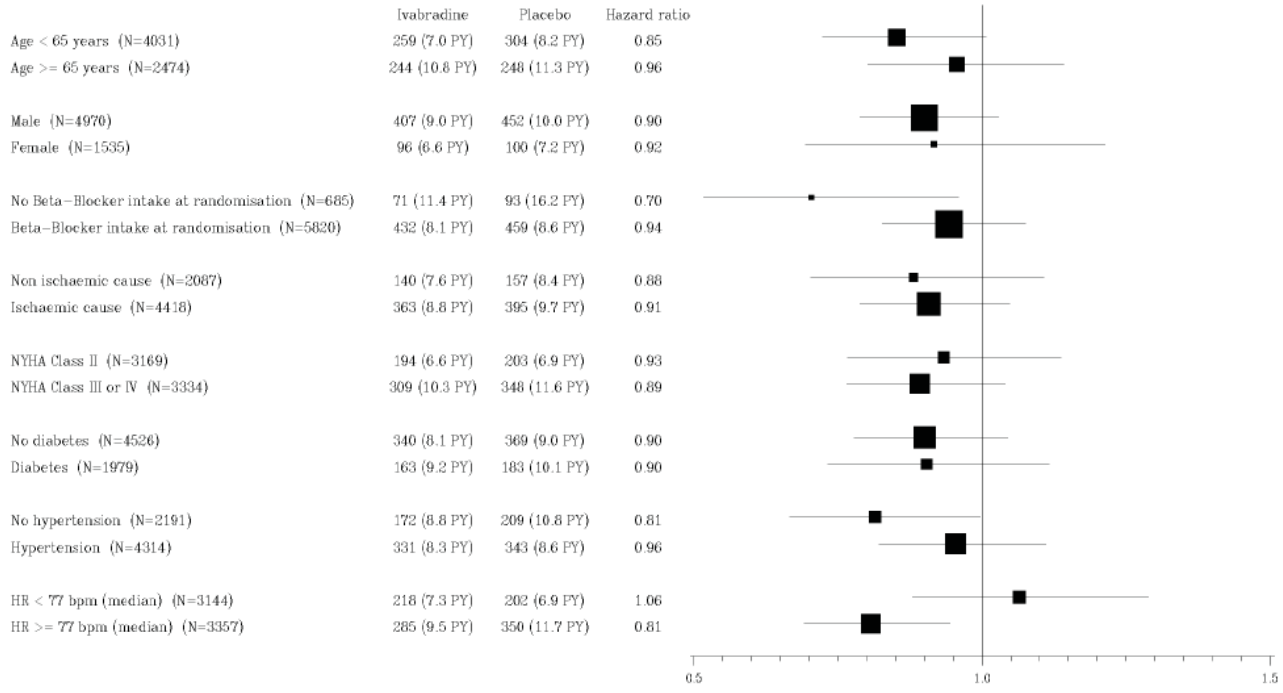


Figure 35. Forest Plot - Estimate of Treatment Effect on CV Death, Pre-defined Subgroups, RS

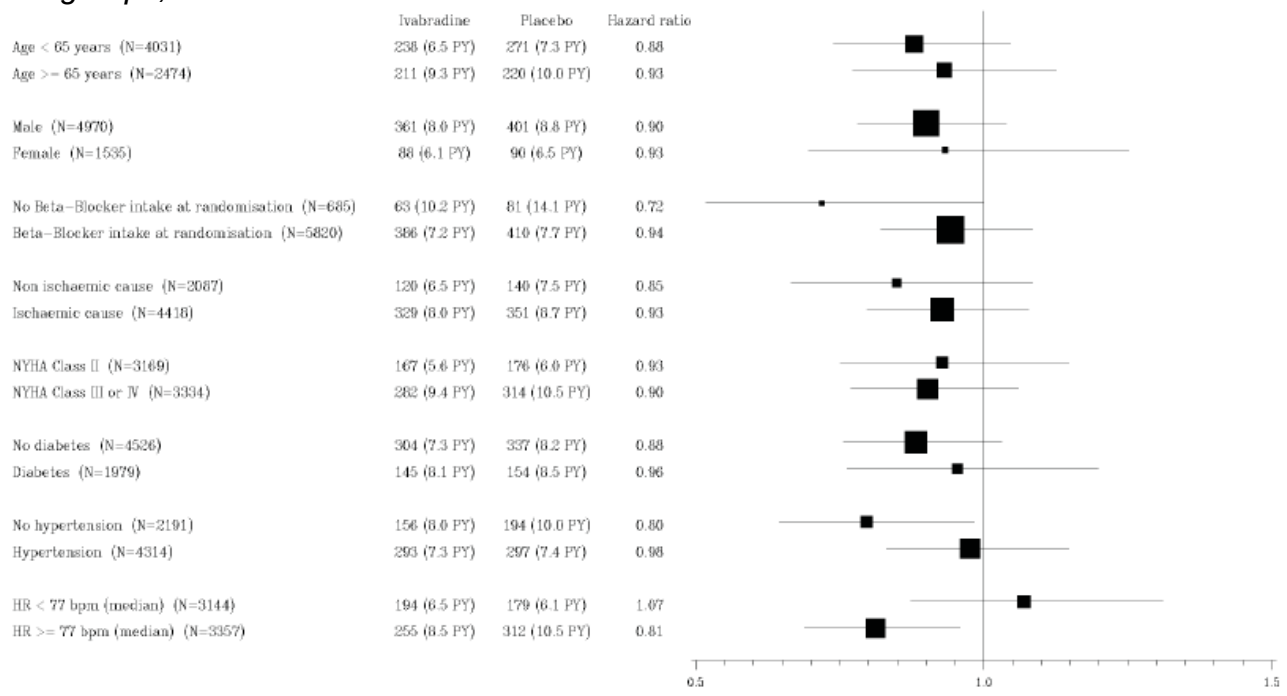
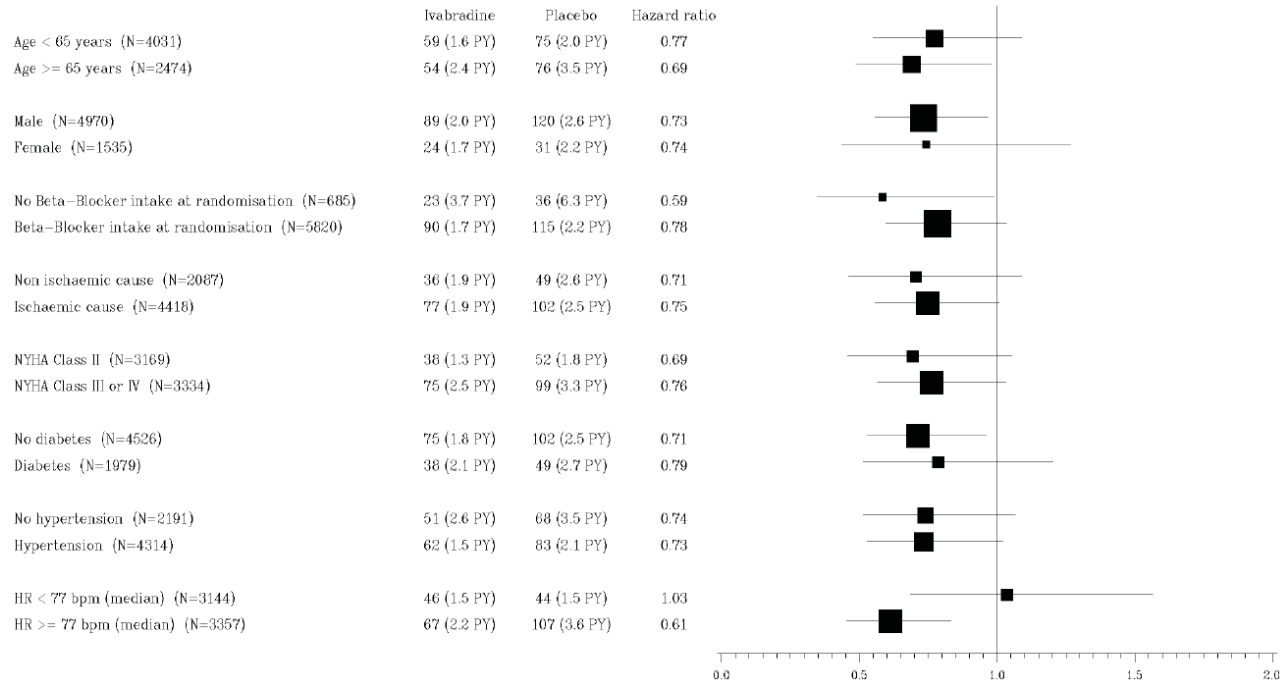


Figure 36. Forest Plot - Estimate of Treatment Effect on Death-HF, Predefined Subgroups, RS



In the RS-BB-dose subset of subjects taking at least 50% of the ESC guideline defined targets for the beta-blockers used in shift, no significant benefit of ivabradine therapy was demonstrated for ACM, Death CV, or Death-HF, as shown in the table below (SHIFT-FSR 124/ 4779):

Table 39. Estimates of Ivabradine Effect on Causes of Death, RS-BB-dose

	Hazard ratio	p-value
	E [95% CI]	
Death from any cause	0.99 [0.81 ; 1.20]	0.922
Cardiovascular death	1.00 [0.81 ; 1.24]	0.986
Death from heart failure	0.84 [0.55 ; 1.30]	0.438

Once again, in the RS-BB-dose subset, the rate of Sudden Cardiac Death (SCD) was slightly higher in the ivabradine treatment group as compared to the placebo treatment group (3.3 %PY versus 2.9 %PY, respectively).

Hospitalizations

The causes for adjudicated hospitalizations are summarized in the table below:

Table 40. FDA SHIFT Analysis: Causes of hospitalizations by treatment, RS

Number of patients with at least one:	Ivabradine (N=3241)		Placebo (N=3264)	
	n	%	n	%
Hospitalization from any cause	1231	38.0	1356	41.5
Hospitalization from CV reason	577	17.8	635	19.5
Hospitalization from WHF	514	15.9	672	20.6
Unplanned hospitalization for any cause	1137	35.1	1264	38.7
Unplanned hospitalization for CV reason	909	28.1	1047	32.1

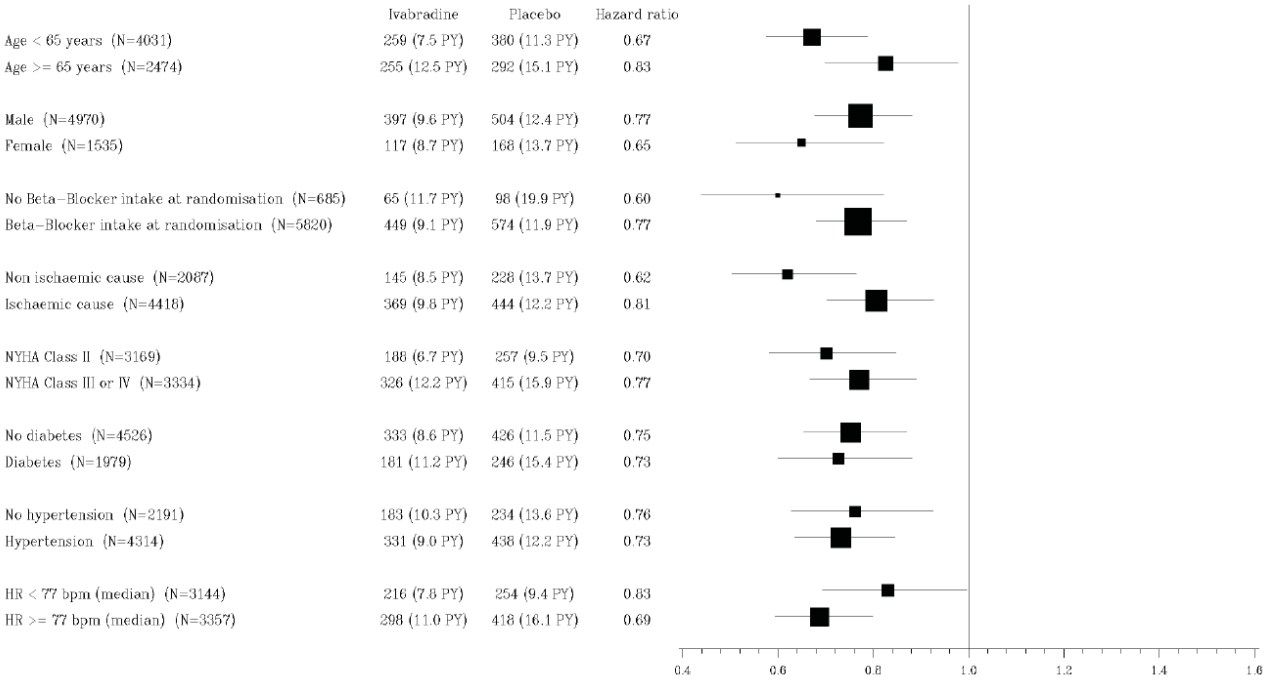
Note that within hospitalization for CV reasons was included hospitalization for acute MI, which happened less frequently in the ivabradine treatment arm than in the placebo treatment arm of SHIFT (1.4 %PY versus 1.5 % PY, respectively). Estimates of the treatment effect of ivabradine on the various causes of hospitalization are given in the following table:

Table 41. FDA SHIFT Analysis: Estimates of Treatment Effect on Causes of Hospitalization, RS

	Hazard Ratio (95% CI)	p-value
Hospitalization from any cause	0.89 [0.82, 0.96]	0.0027
Hospitalization from CV reason	0.85 [0.78, 0.92]	0.0002
Hospitalization from WHF	0.74 [0.66, 0.83]	<0.0001
Unplanned hospitalization for any cause	0.88 [0.81, 0.95]	0.0013
Unplanned hospitalization for CV reason	0.84 [0.77, 0.92]	0.0002

The point estimates of the treatment effect of ivabradine on all predefined subgroups favored ivabradine for hospitalization for WHF, per the forest plot below:

Figure 37. Forest Plot – Estimates of Ivabradine Effect on Hospitalization for WHF, Pre-Defined Subgroups, RS



In contrast to the mortality outcomes for ivabradine therapy group in the RS-BB-dose, the ivabradine treatment group of the RS-BB-dose also demonstrated numerically lower incidences of all hospitalization sub-categories, with significant reductions in Hospitalizations for WHF and CV hospitalizations, and a positive lean for the reduction of hospitalizations for any cause, per the following table (SHIFT FSR 131 / 4779):

Table 42. Estimates of Ivabradine Effect on Hospitalizations, RS-BB-dose

	Hazard ratio	p-value
	E [95% CI]	
Hospitalisation for any cause	0.90 [0.80 ; 1.01]	0.081
Hospitalisation for CV reason	0.88 [0.77 ; 1.00]	**0.0464**
Hospitalisation for worsening heart failure	0.81 [0.67 ; 0.97]	**0.0211**
Unplanned hospitalisation for any cause	0.88 [0.78 ; 0.99]	**0.0352**
Unplanned hospitalisation for CV reason	0.87 [0.76 ; 0.99]	**0.0362**

E: estimate of the hazard ratio between treatment groups (Ivabradine /Placebo) based on an unadjusted Cox proportional hazards model
95% CI: 95% Confidence Interval of the estimate (two-sided)
p-value: Wald test

Composite Secondary Endpoint of CV Death, hospitalization for WHF, or hospitalization for non-fatal MI

The applicant predefined a composite the composite secondary outcome of first event among: CV Death, hospitalization for WHF, or hospitalization for non-fatal MI. The results of this composite outcome for the RS and the RS-BB-dose subsets are as follows:

Table 43. Incidence of Secondary Composite and Estimate of Ivabradine Effect in the RS and RS-BB-dose

	Ivabradine				Placebo				Hazard ratio	p-value
	n/N	(%)	NPY	(%PY)	n/N	(%)	NPY	(%PY)	E [95% CI]	
Randomised Set										
	825/3241	(25.5)	5432	(15.2)	979/3264	(30.0)	5250	(18.7)	0.82 [0.74 ; 0.89]	**< 0.0001**
Randomised Set-BB-dose										
	346/1581	(21.9)	2763	(12.5)	381/1600	(23.8)	2699	(14.1)	0.89 [0.77 ; 1.03]	0.124

n: number of patients having experienced the endpoint; N: number of patients at risk
%: global incidence rate = (n/N) x 100; NPY: number of patient-years at risk; %PY: annual incidence rate = (n/NPY) x 100
E: estimate of the hazard ratio between treatment groups based on an adjusted Cox proportional hazards model with beta-blocker intake at randomisation as a covariate; 95% CI: 95% Confidence Interval of the estimate (two-sided)
p-value: Wald test

Reviewer's Comment: the applicant correctly points out that the positive result in the RS for this composite outcome is driven by CV Death and Hospitalization for WHF (the primary composite endpoint), which in this analysis overwhelmed the few hospitalizations for acute MI that occurred in SHIFT (33 (2.1%) in the ivabradine treatment arm versus 37 (2.3%) in the placebo treatment arm).

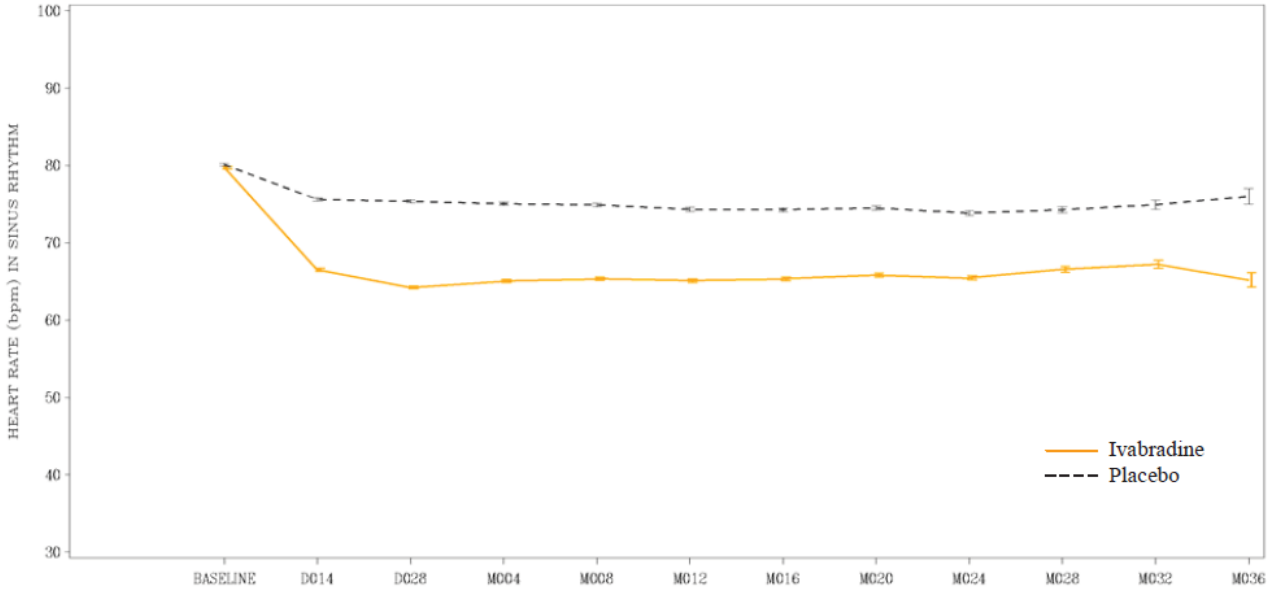
6.1.6 Other Endpoints

Heart Rate

Resting HR was measured by resting 12 lead-ECG at each clinic visit. Resting HR for the RS and the RS-BB-dose were both approximately 80 bpm (somewhat attesting to inadequate beta-blockade in both populations, understanding there are extenuating circumstances that limit what physicians can achieve with beta-blocker doses, as discussed in section 6 summary of efficacy).

The response to ivabradine was a lowering of HR that was similar in the RS and the RS-BB-dose groups over time, as seen in the figures below:

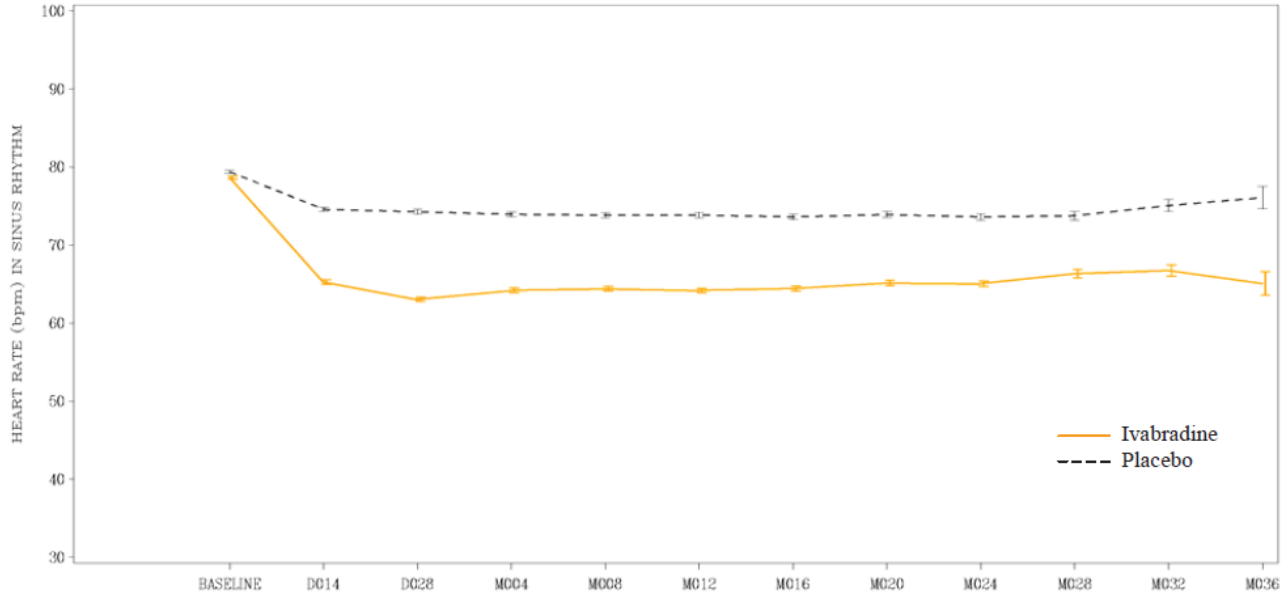
Figure 38. Mean Heart Rate by Visit, RS



number of patients with a value observed at baseline and at the considered visit

Ivabradine	3240	3181	3147	3028	2880	2727	2479	2215	1732	1020	530	156
Placebo	3261	3203	3182	3070	2893	2765	2479	2199	1724	1028	535	183

Figure 39. Mean Heart Rate by Visit, RS-BB-dose



number of patients with a value observed at baseline and at the considered visit

Ivabradine	1581	1556	1540	1482	1434	1361	1253	1134	945	535	260	74
Placebo	1597	1572	1566	1524	1445	1390	1251	1127	936	518	260	94

<u>Reviewer's Comment</u>: These stable looking heart rate curves may in fact be an artifact of the protocol, and not the natural stable behavior of ivabradine. Recall that the protocol mandated the removal of subjects with heart rates consistently less than 50 bpm or those experiencing symptomatic bradycardia. Therefore, the subjects with the slowest heart rates were removed from the trial and did not contribute to the curves for ivabradine in Figure 39 and 40 above.

In contrast, on drug initiation, it appeared as though the incidence of ivabradine-induced bradycardia continuously escalated in the first 28 days of therapy, as did the incidence of bradycardia adverse events. (see Figure 58 and Figure 59 below in the safety section). These curves are also somewhat artificial, in that they reflect the protocol-driven dose increases in most patients at the time of the week 2 visit.

An analysis of HR behavior after initiation in patients who did not change their dose will be helpful in delineating the true long-term heart rate response profile to fixed doses of ivabradine.

The Between-group difference in change of heart rate between baseline and D028 and between baseline and last post-randomization visit in the RS and RS-BB-dose are shown in the following table (SHIFT FSR : 135 / 4779):

Table 44. Between-group Difference in Change of HR between Baseline and D028 and between Baseline and Last Post-randomization Visit in the RS and RS-BB-dose

		Randomised Set		Randomised Set-BB-dose	
		Ivabradine (N = 3241)	**Placebo (N = 3264)**	**Ivabradine (N = 1581)**	**Placebo (N = 1600)**
	n	3146	3182	1540	1566
Baseline	Mean ± SD	79.6 ± 9.4	80.0 ± 9.6	78.5 ± 8.4	79.3 ± 8.8
	Min ; Max	48 ; 130	58 ; 142	48 ; 122	60 ; 130
D028	Mean ± SD	64.2 ± 11.1	75.4 ± 12.4	63.1 ± 10.6	74.3 ± 11.9
	Min ; Max	38 ; 125	40 ; 130	38 ; 125	40 ; 122
D028 - Baseline	Mean ± SD	-15.4 ± 10.7	-4.6 ± 10.6	-15.5 ± 10.7	-5.1 ± 10.7
	Min ; Max	-73 ; 28	-52 ; 45	-73 ; 28	-52 ; 38
Statistical analysis	E (SE)	-10.9 (0.3)		-10.8 (0.4)	
	95% CI	[-11.4 ; -10.4]		[-11.5 ; -10.0]	
	n	3209	3228	1569	1582
Baseline	Mean ± SD	79.7 ± 9.5	80.0 ± 9.7	78.6 ± 8.5	79.4 ± 8.9
	Min ; Max	48 ; 130	58 ; 142	48 ; 122	60 ; 130
Last post randomisation	Mean ± SD	67.7 ± 12.9	75.9 ± 13.5	66.6 ± 12.3	75.1 ± 13.1
	Min ; Max	40 ; 141	40 ; 136	42 ; 137	44 ; 130
Last post randomisation – Baseline	Mean ± SD	-12.0 ± 13.3	-4.1 ± 12.9	-12.0 ± 12.8	-4.3 ± 12.6
	Min ; Max	-69 ; 59	-67 ; 44	-69 ; 59	-47 ; 40
Statistical analysis	E (SE)	-8.1 (0.3)		-8.1 (0.4)	
	95% CI	[-8.7 ; -7.5]		[-8.9 ; -7.3]	

NYHA Classification

In both the ivabradine and the placebo treatment arms of the RS, there were increases in the proportions of NYHA classes I and II during the study. Class shifts were assessed in the categories of improvement, stability, or worsening. Chi-2/complementary analysis of the distribution of these shifts toward improvement was non-statistically higher for the ivabradine treatment arm of the RS-BB-dose, and improvement showed a statistically significant improvement in the RS. The results of this analysis for the RS and the RS-BB-dose are shown in the table below (SHIFT FSR 137 / 4779):

Table 45. NYHA Classification – Change of Class from Baseline to last Post-randomization Visit, RS and RS-BB-dose

		Randomised Set		Randomised Set-BB-dose	
		Ivabradine (N = 3241)	Placebo (N = 3264)	Ivabradine (N = 1581)	Placebo (N = 1600)
All	**n**	**3216**	**3234**	**1570**	**1585**
Improvement	n' (%)	887 (27.6)[1]	776 (24.0)[1]	407 (25.9)[2]	384 (24.2)[2]
Stability	n' (%)	2172 (67.5)	2265 (70.0)	1094 (69.7)	1120 (70.7)
Worsening	n' (%)	157 (4.9)	193 (6.0)	69 (4.4)	81 (5.1)

n: number of evaluable patients; % = (n'/n) x 100
[1] *Chi-2 test: p = 0.0010, complementary test (ivabradine versus placebo)*
[2] *Chi-2 test: p = 0.272, complementary test (ivabradine versus placebo)*

Global Assessments of HF symptoms

Both patients and physicians assessed the patients' conditions as improvement, stability, or worsening at the last post-baseline visit, using chi-2/complementary testing, with the results as follows (SHIFT FSR 139 / 4779):

Table 46. Global assessment - Class at last post-Randomization Visit -RS and RS-BB-dose

		Randomised Set		Randomised Set-BB-dose	
		Ivabradine (N = 3241)	Placebo (N = 3264)	Ivabradine (N = 1581)	Placebo (N = 1600)
Patient Global Assessment					
All	**n**	**2951**	**2982**	**1462**	**1496**
Improvement	n' (%)	2118 (71.8)[1]	2017 (67.6)[1]	1041 (71.2)[3]	1013 (67.7)[3]
Stability	n' (%)	633 (21.5)	738 (24.8)	325 (22.2)	378 (25.3)
Worsening	n' (%)	200 (6.8)	227 (7.6)	96 (6.6)	105 (7.0)
Physician Global Assessment					
All	**n**	**3091**	**3108**	**1518**	**1543**
Improvement	n' (%)	1888 (61.1)[2]	1772 (57.0)[2]	916 (60.3)[4]	869 (56.3)[4]
Stability	n' (%)	954 (30.9)	1043 (33.6)	479 (31.6)	552 (35.8)
Worsening	n' (%)	249 (8.1)	293 (9.4)	123 (8.1)	122 (7.9)

n: number of evaluable patients; % = (n'/n) x 100
[1] *Chi-2 test: p = 0.0005, complementary test (ivabradine versus placebo)*
[2] *Chi-2 test: p = 0.0011, complementary test (ivabradine versus placebo)*
[3] *Chi-2 test: p = 0.0394, complementary test (ivabradine versus placebo)*
[4] *Chi-2 test: p = 0.0240, complementary test (ivabradine versus placebo)*

Per the applicant's analysis, "*In the RS, the rate of patients having an improvement in global assessment at the last post-randomization visit was statistically significantly higher in the ivabradine group than in the placebo group for patient-reported assessment (71.8%*

versus 67.6%, p = 0.0005, complementary test) as well as for the physician-reported assessment (61.1% versus 57.0%, p = 0.0011, complementary test). Similar results were observed in the RSBBdose."

6.1.7 Subpopulations

SHIFT PCE Outcomes by beta-blocker Dose

In section 6.1.4 above the PCE and its components were assessed with respect to no-beta-blocker, any-beta-blocker, or at least 50% of ESC guideline-recommended dosing targets for beta-blockers used during the trial. The overall impressions of those "large-bucket" analyses were that the ivabradine effects were diminished overall as baseline beta-blocker dose increased. In this FDA analysis, the outcomes of the PCE and components were assessed in a more rigorous way, which demonstrates an unequivocal inverse "dose response" (with respect to background beta-blocker use) for the treatment effect of ivabradine on the PCE, hospitalization for WHF, and CV death, based on percentages of guideline-directed target that beta-blocker therapy was present in at baseline, per Table 47 below. For all outcomes, ivabradine shows significant efficacy only as background beta-blocker dose declines. Of note, adding ivabradine to full dose beta-blockers produced an estimate of the hazard ratio for ivabradine effect on CV death that was greater than 1.0, but not statistically significant.

Table 47. FDA SHIFT Analysis: Estimates of Ivabradine Treatment Effect on the PCE, Hopitalization for WHF, and CV Death by BB Dose at Baseline, RS, all Beta-Blockers Used in SHIFT

	Ivabradine	Placebo	HR (95% CI)	P-value
	n (%)	n (%)		
Primary Endpoint				
No BB	101 (29.4)	134 (39.3)	0.68 (0.52, 0.88)	0.003
BB < 25%	148 (30.8)	171 (40.0)	0.74 (0.60, 0.93)	0.008
BB 25% to 50%	204 (26.2)	260 (30.8)	0.81 (0.68, 0.98)	0.029
BB 50% to 100%	181 (21.6)	212 (24.8)	0.84 (0.69, 1.02)	0.077
BB >= 100%	149 (20.1)	150 (20.1)	0.99 (0.79, 1.24)	0.904
Hosp for WHF				
No BB	65 (18.9)	98 (28.7)	0.60 (0.44, 0.82)	0.001
BB < 25%	99 (20.6)	125 (29.3)	0.68 (0.52, 0.88)	0.004
BB 25% to 50%	131 (16.8)	183 (21.7)	0.75 (0.60, 0.93)	0.01
BB 50% to 100%	124 (14.8)	154 (18.0)	0.79 (0.62, 1.00)	0.05
BB >= 100%	89 (12.0)	106 (14.2)	0.84 (0.63, 1.11)	0.21
CV death				
No BB	63 (18.3)	81 (23.8)	0.72 (0.52, 1.00)	0.05
BB < 25%	84 (17.5)	96 (22.5)	0.81 (0.61, 1.09)	0.163
BB 25% to 50%	119 (15.3)	134 (15.9)	0.94 (0.74, 1.21)	0.637
BB 50% to 100%	96 (11.5)	101 (11.8)	0.95 (0.72, 1.25)	0.702
BB >= 100%	80 (10.8)	74 (9.9)	1.08 (0.79, 1.48)	0.646

This analysis, when repeated to assess the treatment effect of ivabradine on the PCE and its components, on a background of differing intensities of beta-blocker therapy with only those beta-blockers that are approved in the US for treating HFrEF (bisoprolol, carvedilol, and metroprolol succinate), the inverse relationship between background beta-blocker intensity and ivabradine efficacy was again demonstrated for the PCE and both of its components, as shown in Table 48 below. Once again, adding ivabradine to full dose beta-blockers produced an estimate of the hazard ratio for ivabradine effect on CV death that was greater than 1.0, but not statistically significant.

Table 48. FDA SHIFT Analysis: Estimates of Ivabradine Treatment Effect on the PCE, Hospitalization for WHF, and CV Death by BB Dose at Baseline, RS, Beta-Blockers Approved for the CHF Indication in the United States

	Ivabradine	Placebo	HR (95% CI)	P-value
	n (%)	n (%)		
Primary Endpoint				
No BB	101 (29.4)	134 (39.3)	0.68 (0.52, 0.88)	0.003
BB < 25%	126 (32.1)	155 (43.2)	0.71 (0.56, 0.89)	0.004
BB 25% to 50%	174 (26.4)	220 (31.0)	0.82 (0.67, 0.995)	0.0449
BB 50% to 100%	159 (22.8)	170 (24.3)	0.91 (0.73, 1.13)	0.381
BB >= 100%	138 (19.9)	139 (20.1)	0.98 (0.78, 1.25)	0.896
Hosp for WHF				
No BB	65 (18.9)	98 (28.7)	0.60 (0.44, 0.82)	0.001
BB < 25%	86 (21.9)	112 (31.2)	0.67 (0.50, 0.89)	0.0049
BB 25% to 50%	117 (17.8)	158 (22.3)	0.77 (0.60, 0.97)	0.028
BB 50% to 100%	112 (16.1)	123 (17.6)	0.89 (0.69, 1.14)	0.35
BB >= 100%	80 (11.6)	97 (14.0)	0.82 (0.61, 1.10)	0.19
CV death				
No BB	63 (18.3)	81 (23.8)	0.72 (0.52, 1.00)	0.05
BB < 25%	71 (18.1)	92 (25.6)	0.72 (0.53, 0.99)	0.041
BB 25% to 50%	100 (15.2)	112 (15.8)	0.94 (0.72, 1.23)	0.656
BB 50% to 100%	83 (11.9)	84 (12.0)	0.96 (0.71, 1.31)	0.809
BB >= 100%	75 (10.8)	71 (10.3)	1.05 (0.76, 1.46)	0.755

SHIFT outcomes and Digoxin

Ivabradine's effect on I_f is rate dependent. Therefore, there is the possibility to any or all negative chronotropes (beta-blockers and others), may attenuate its benefits. In SHIFT, 22% of patients were on digoxin at baseline, and this percentage increased slightly during the course of the trial. Accordingly, FDA analyzed the SHIFT PCE for all randomized patients who were digitalized at baseline. Ivabradine did not show significant efficacy in the sub-group of digitalized patients (though the p-value for interaction was not significant), as shown in the following table:

Table 49. FDA SHIFT Analysis: Estimates of Treatment Effect on the PCE by Digoxin Treatment at Baseline, RS+Polish Sites

Digoxin Cotherapy	**Ivabradine**		**Placebo**		**HR (95% CI)**	**p-value**
	n/N	%	n/N	%		
No	547/2560	21.4	671/2574	26.1	0.78 (0.70, 0.88)	<0.0001
Yes	250/706	35.4	269/711	37.8	0.92 (0.78, 1.10)	0.816

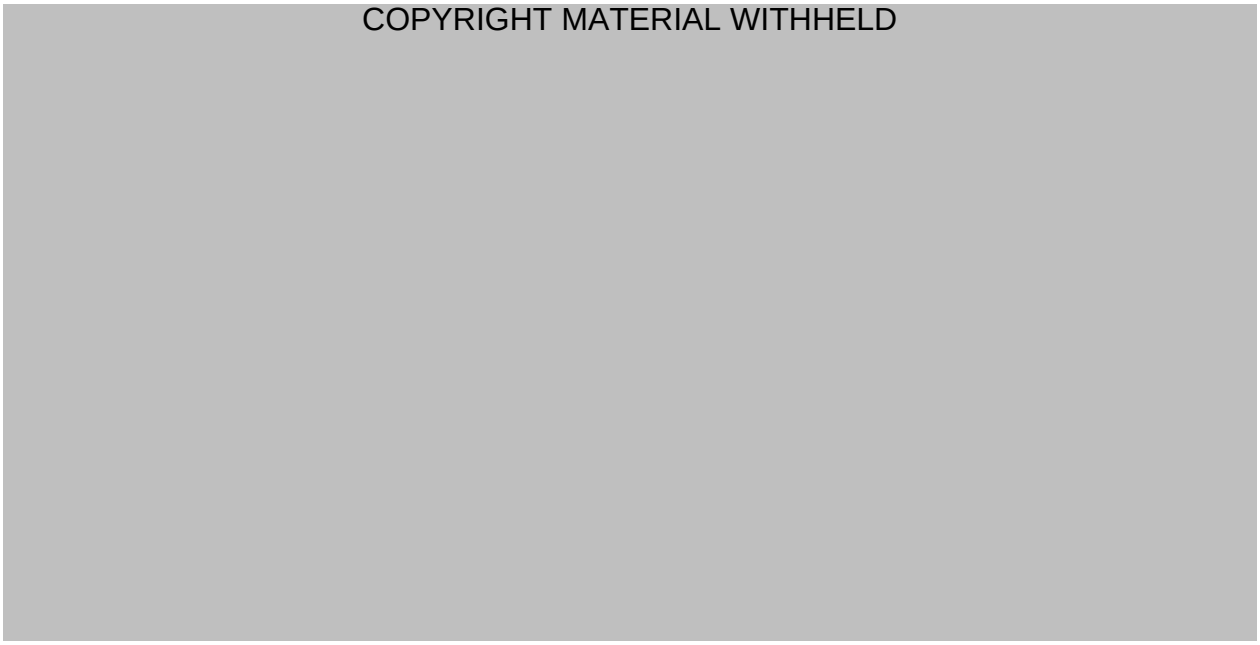
SHIFT Treatment Effect by Baseline Heart Rate (See Section 6.1.5, Death)

In the FDA analysis of adjudicated death in section 6.1.5, it was noticed that in the subgroup of patients with a heart rate < 77 bpm (the median baseline heart rate in SHIFT) in the RS, the point estimate for ivabradine treatment effect was greater than 1 for all-cause death, death due to WHF, and CV death (interaction p-value 0.0379 for HR < 77 bpm and CV death).

Of note, this is not the first time that a potentially negative effect of ivabradine therapy on CV mortality in patients with low baseline resting heart rates has been noticed. Around the time that SHIFT results were published, Bohm et al published an analysis of outcomes from SHIFT based on quintiles of resting heart rate. From that publication, for the cardiovascular death component of the PCE, patients with a resting HR from 72-75 demonstrated an increase in CV mortality with ivabradine therapy, as shown in the figure below that was excerpted from that paper[6]:

[6] Bohm M et al. Lancet 2010; 376: 886–94

Figure 40. Effect of ivabradine compared with placebo on (A) the primary composite endpoint, (B) first hospital admissions for worsening heart failure, and (C) cardiovascular deaths in the whole patient population, defined by quintiles of baseline heart-rate distribution



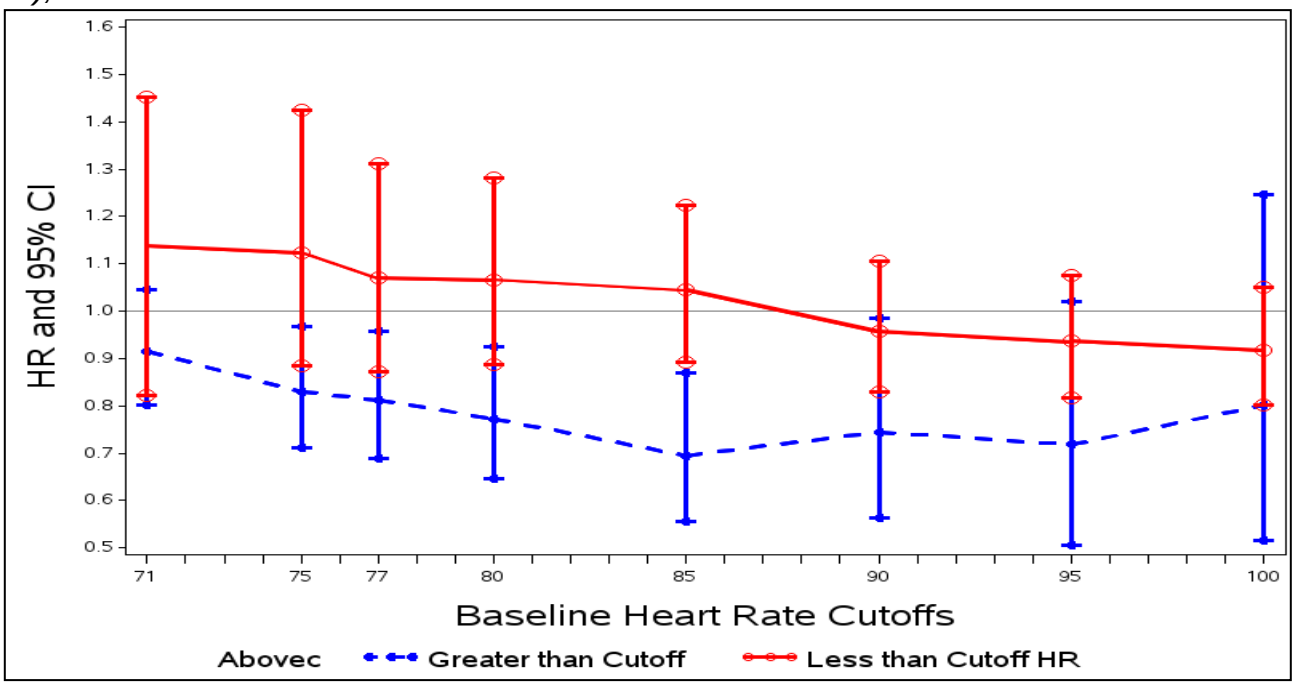
Bohm M et al. Lancet 2010; 376: 886–94

These observations raised the possibility that patients with the slowest baseline heart rates might be more sensitive to ivabradine's rate slowing effects (even though the drug demonstrates use dependent rate slowing in-vitro). Consideration was given to a drug interaction with the highest doses of beta-blockers (patients who may also demonstrate the lowest heart rates) causing an excess of CV death (hazard ratio 1.08 in table 47 above, but not statistically significant). In addition, it was noted that that the point estimate for the hazard ratio of treatment effect is also greater than 1 for hospitalization due to WHF for subjects > 65 years of age in the RS-BB-dose (p-value for interaction 0.0127, data not shown). Thus, a careful assessment of the SHIFT data for the effect of ivabradine by resting heart rate cutoffs and by age cutoffs was performed.

Accordingly, FDA further explored the relationship of the point estimate for the hazard ratio of the ivabradine treatment effect in SHIFT across a wide range of heart rate cutoffs (above and below the cutoff) and age cutoffs (above and below the cutoff), to assess ivabradine effects on the SHIFT PCE and its components, as well as for all-cause mortality. The first set of plots displays outcomes by baseline mean heart rate, and demonstrates the following:

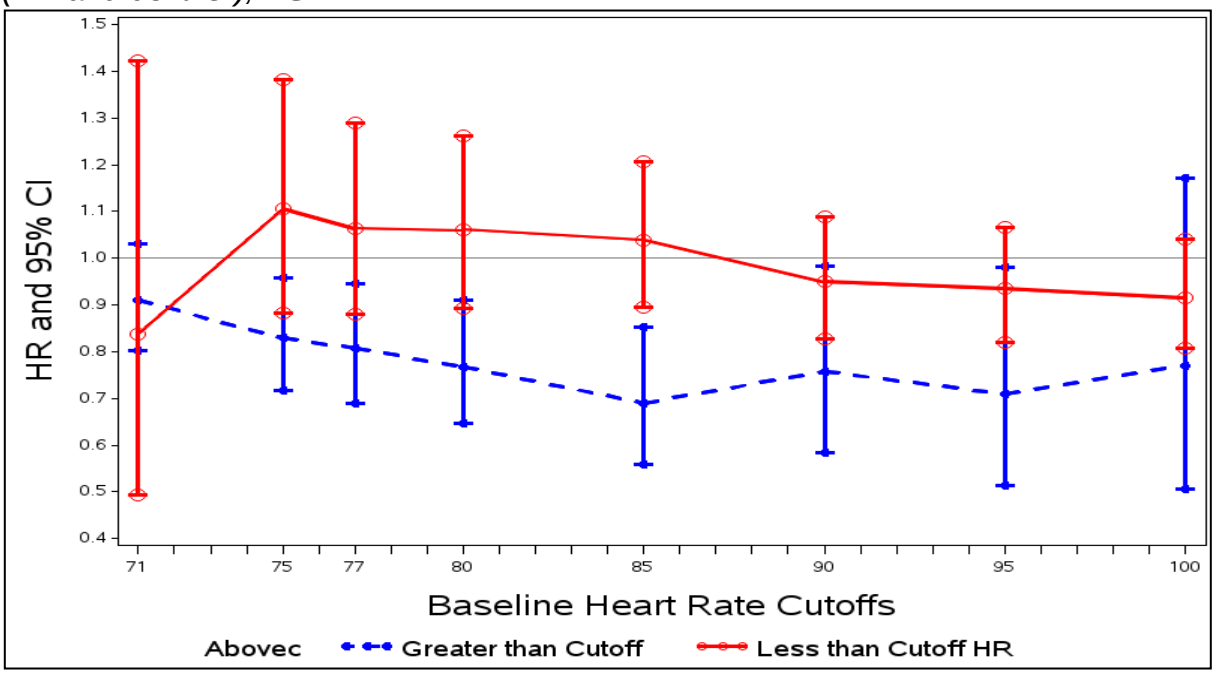
- The point estimates for the hazard ratio of the ivabradine effect on CV death are greater than 1.0 for baseline heart rates ≤ 85 bpm (Figure 41 below):

Figure 41. FDA SHIFT Analysis: CV Death by Baseline Heart Rate Cutoffs (HR and 95% CI), RS



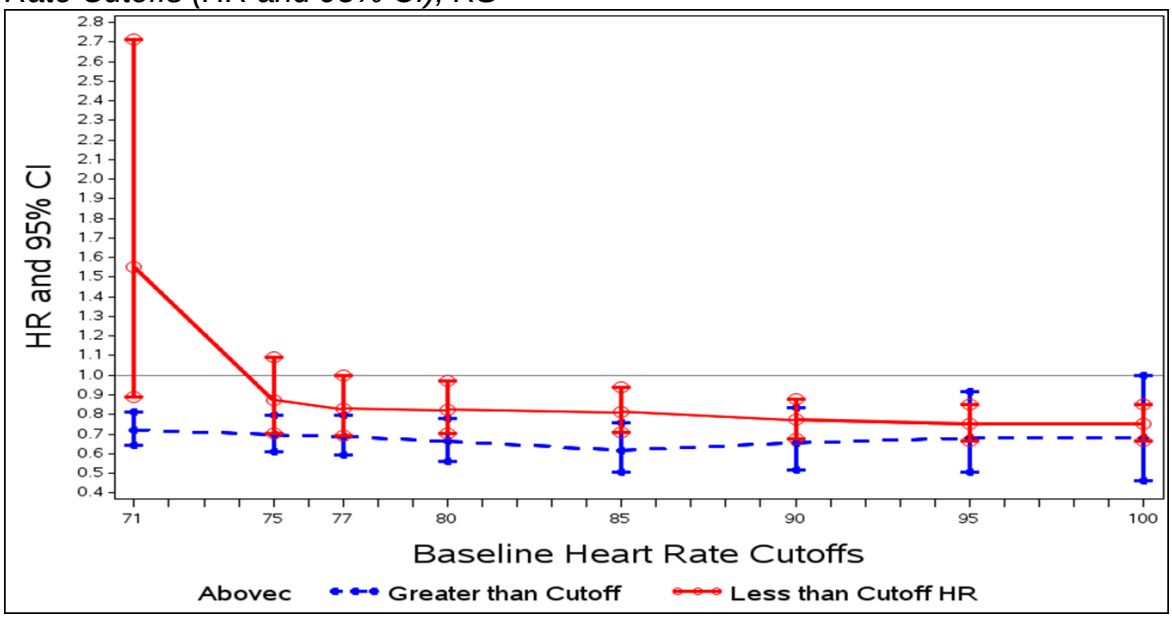
- The point estimates for the hazard ratio of the ivabradine effect on all-cause death are also greater than 1.0 for baseline heart rates ≤ 85 bpm (Figure 42 below):

Figure 42. FDA SHIFT Analysis: SHIFT All-cause Death by Baseline Heart Rate Cutoffs (HR and 95% CI), RS



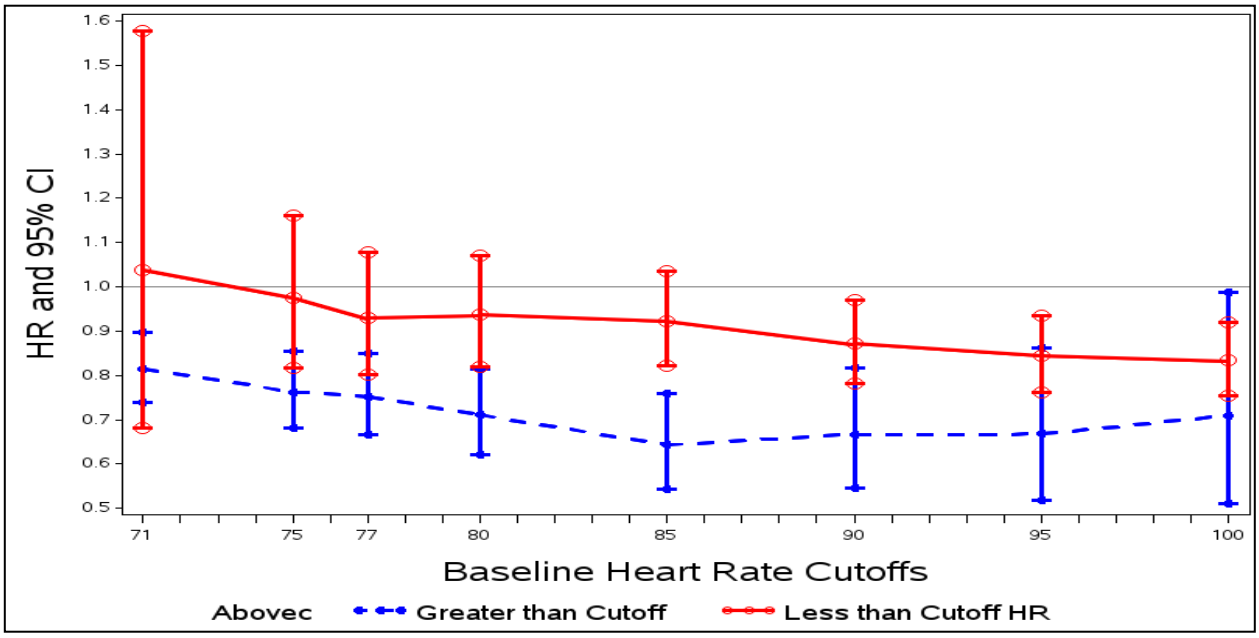
- The point estimate for the hazard ratio of the ivabradine effect on hospitalization due to WHF is greater than 1.0 for baseline heart rates < 75 bpm (Figure 44 below):

Figure 43. FDA SHIFT Analysis: SHIFT Hospitalization due to WHF by Baseline Heart Rate Cutoffs (HR and 95% CI), RS



- The PCE cutoff curves are a fusion of the mortality and hospitalization curves, and can obscure what is happening to the individual subcomponents of the endpoint composite, but have the advantage of demonstrating the relative risk of experiencing either CV death or hospitalization for WHF, as follows:
    - Hospitalization for WHF pulls the “below cutoff” red curve down below unity for heart rates 75-85
    - The point estimate for the hazard ratio of the ivabradine effect on the PCE is therefore < 1.0 for heart rates as low as 75 bpm (Figure 45 below):

Figure 44. FDA SHIFT Analysis: PCE by Baseline Heart Rate Cutoffs (HR and 95% CI), RS



- For the age analysis, there was no age above which the point estimates for the hazard ratios of the ivabradine effects on any of the four outcomes (CV death, all-cause death, hospitalization for WHF, or the PCE) were not below one (Figure 45, Figure 46, Figure 47,and Figure 48, respectively, with
- Figure 49 showing a second type of age versus PCE display):

Figure 45. FDA SHIFT Analysis: CV Death by Baseline Age Group Cutoffs (HR and 95% CI), RS

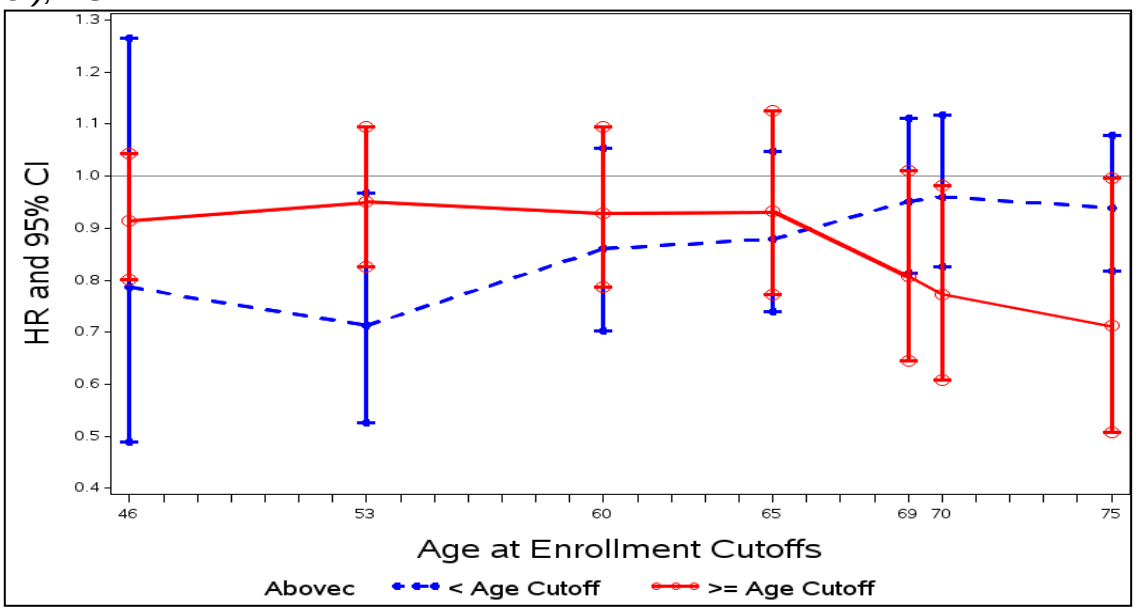


Figure 46. FDA SHIFT Analysis: All-cause Death by Baseline Age Group Cutoffs (HR and 95% CI), RS

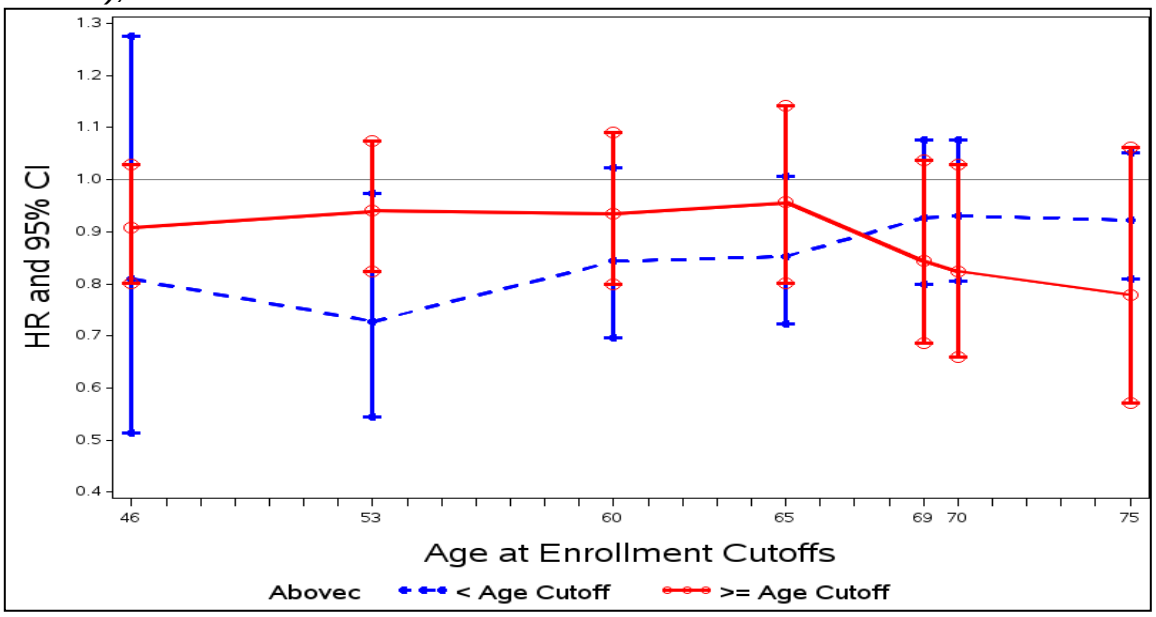


Figure 47. FDA SHIFT Analysis: Hospitalization for WHF by Baseline Age Group Cutoffs (HR and 95% CI), RS

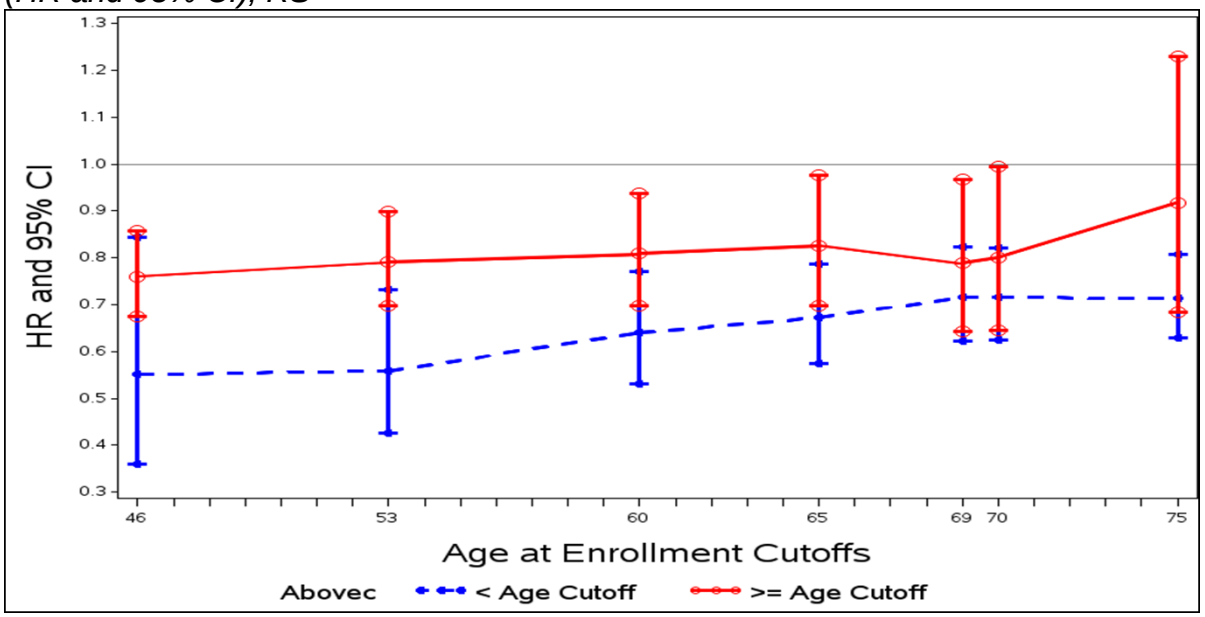


Figure 48. FDA SHIFT Analysis: PCE by Baseline Age Group Cutoffs (HR and 95% CI)

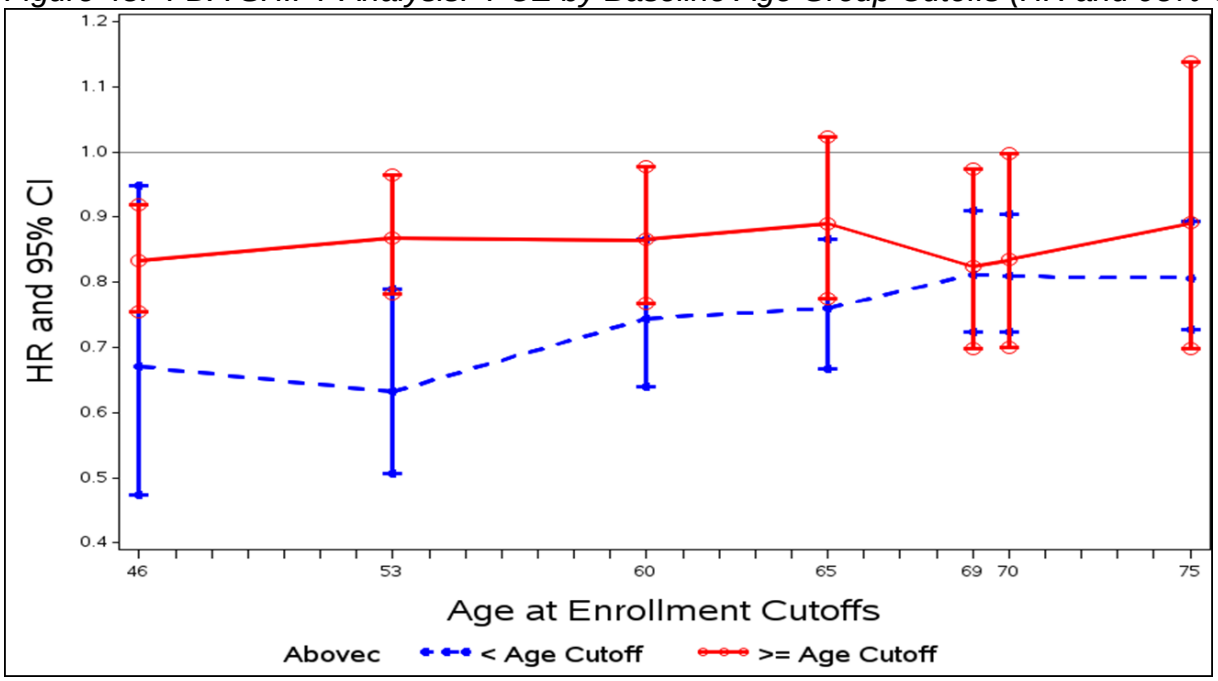
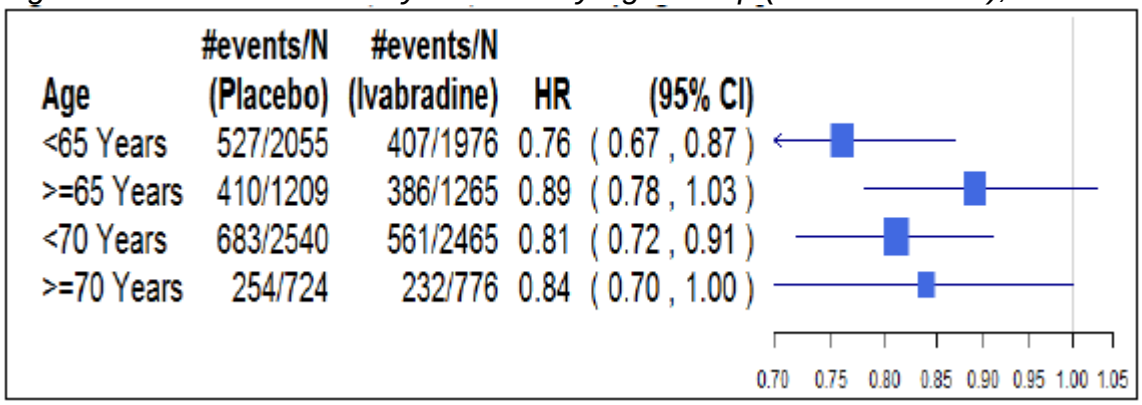


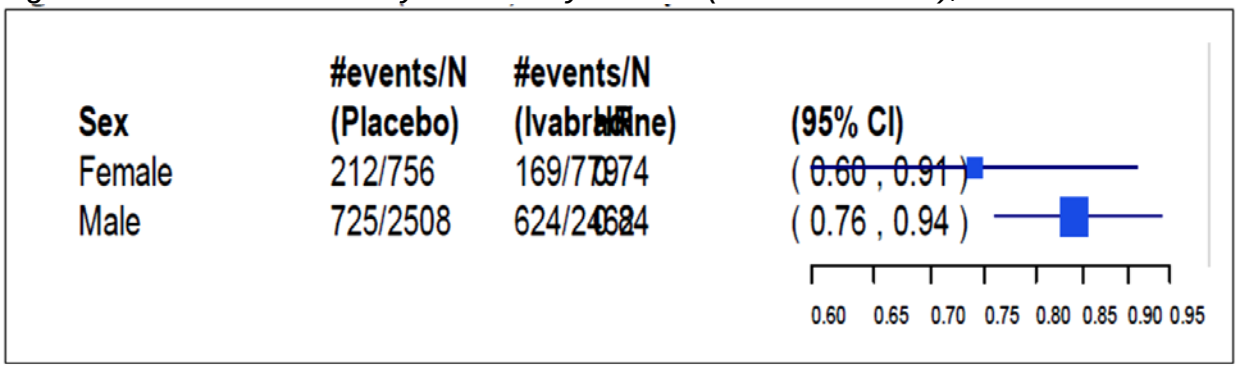
Figure 49. FDA SHIFT Analysis: PCE by Age Group (HR and 95%CI), RS



SHIFT Outcomes by Gender

No obvious differences in the hazard ratios for the primary endpoint were seen comparing the two gender groups, per the figure below:

Figure 50. FDA SHIFT Analysis: PCE by Gender (HR and 95% CI), RS



6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

- Consider starting all patients with heart rates below 85 (or age ≥ 75 years) on the 2.5mg BID dose and carefully titrated upward to clinical effect.
- Patients with resting heart rates above 85 can be started on 5.0 mg BID
- Consider raising minimum heart rate for patient selection to 75 bpm.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of effect is confirmed by sequential measurements of heart rate over time in the SHIFT study (Figures 39 and 40 above).

Withdrawal effects: In follow-up to the Division's discussion with the sponsor on this topic, the sponsor responded as follows:

> Three studies in patients with angina were designed with a 1- to 2-week placebo run-out period: studies CL2-009 (NP07497), CL3-017 (NP15194), and CL3-019 (NP15390). The presence of a rebound phenomenon with abrupt ivabradine discontinuation was assessed through the integrated analysis of 609 subjects from these studies (Sub Safety Set Rebound phenomenon). There was no obvious rebound effect after abrupt stopping of ivabradine treatment (Section 5.7 of Module 2.7.4). Upon cessation of treatment, heart rate returned rapidly toward baseline values during a 1-week placebo-controlled withdrawal phase as illustrated in Study CL2-009.
>
> > *Reviewer's Comment: The location that the applicant points to for this integrated assessment is incorrect (Section 5.7 of Module 2.7.4 is in fact the location of the above-written paragraph itself in the submission. However, the three studies that are referred to concluded the following about withdrawal effects:*
>
> *Np07497 – "In conclusion, this double-blind placebo-controlled run-out period of a multicentric, multinational, phase II study showed that after 2 or 3 months, S 16257 at 10 mg bid on monotherapy is stiI efficient on ischemia and ischemic symptoms as demonstrated by Err, without pharmacological tolerance, whereas treatment withdrawal rapidly led to a marked deterioration of these symptoms. No rebound phenomenon was observed after treatment withdrawal" (as assessed by the lack of serious cardiac events reported after treatment withdrawal suggesting the absence of rebound phenomena."*
>
> *NP15194 – Lack of rebound assess be description of the number of angina attacks and short acting nitrates taken after ivabradine discontinuation in this angina study. "…the mean number of angina attacks per week during the run-out period was lower than the mean observed during the run-in period suggesting that the benefit was sustained over the two-week run-out period… Similar results were observed for the mean consumption of short acting nitrates."*
>
> *NP15390 – Rebound was also assessed by frequency of anginal attacks and intake of short acting nitrates during treatment withdrawal in this study. "The mean changes in the mean number of angina attacks and mean consumption of short*

acting nitrates per week between the last post-M0 period and the run-out period showed a slight increase in the ivabradine group, and no change in the atenolol group: 0.35 ± 1.35 and 0.25 ± 1.3 versus -0.04 ± 1.08 and 0.04 ± 0.65 respectively. However, the mean number of angina attacks and the mean consumption of short acting nitrates per week did not reach the values observed at the end of the run-in period in the ivabradine group (2.08 ± 4.38 and 0.95 ± 2.26 respectively at the end of the run-in period and 0.85 ± 1.86 and 0.58 ± 1.69 respectively at the end of the run-out period)."

Potential of abuse was assessed by the applicant as follows (SHIFT clinical overview pg 81): *In the nonclinical program and in the clinical development of ivabradine, no specific pharmacodependency study was performed since the receptor-binding profile of ivabradine did not raise any concern with regards to a potential drug dependency. In the long-term studies of the preclinical program, no sign of potential dependency was observed in animals during the off-dose period, and in phase 2 and phase 3 clinical trials, there was no case of drug abuse or drug seeking behavior. In the post marketing setting, there was no report related to abuse. The potential for drug abuse with ivabradine is considered to be negligible.*

6.1.10 Additional Efficacy Issues/Analyses

DATA integrity and Robustness of the SHIFT Result

An unusual feature of the SHIFT mortality data was noticed early in the review. Specifically, at the 69 sites that enrolled a single subject who ultimately died (in other words, single enrollment with 100% mortality), the point estimate of the hazard ratio for ivabradine treatment effect was incredibly good for both all-cause Death and CV death. Furthermore, their appeared to be an inverse "dose effect" on death, whereby the more patients that enrolled, the less impressive the death outcome seemed to be, per Figure 52 and Figure 53 for all-death and CV death, respectively:

Figure 51. FDA SHIFT Analysis: ALL-cause Death by Center Enrollments (HR and 95% CI), RS

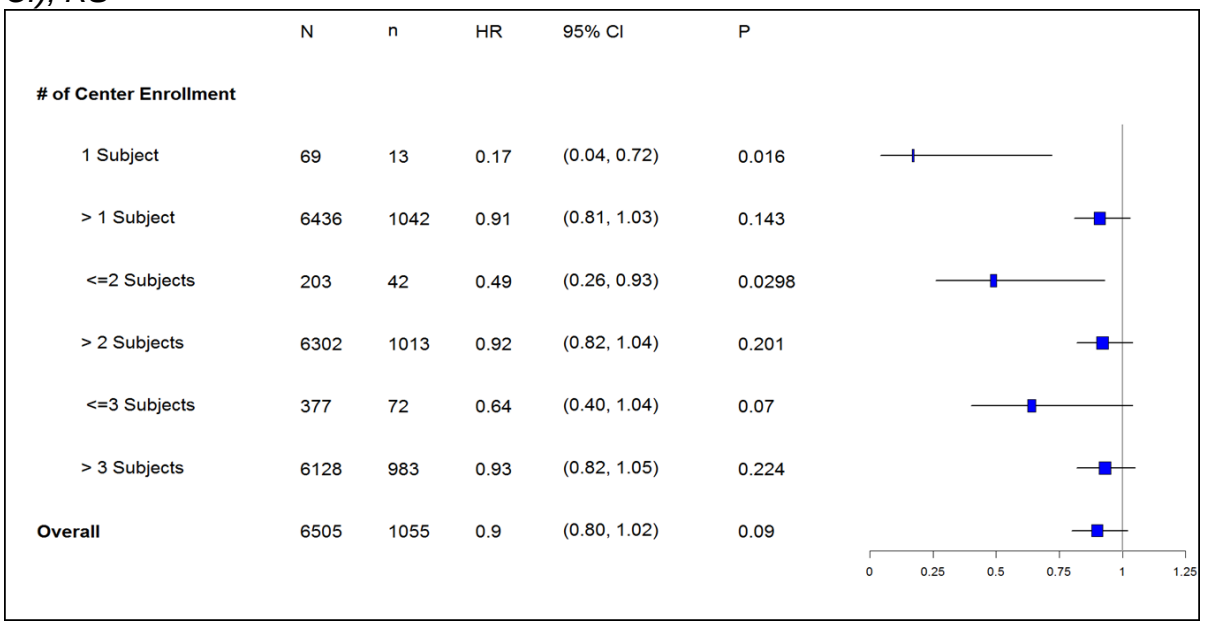
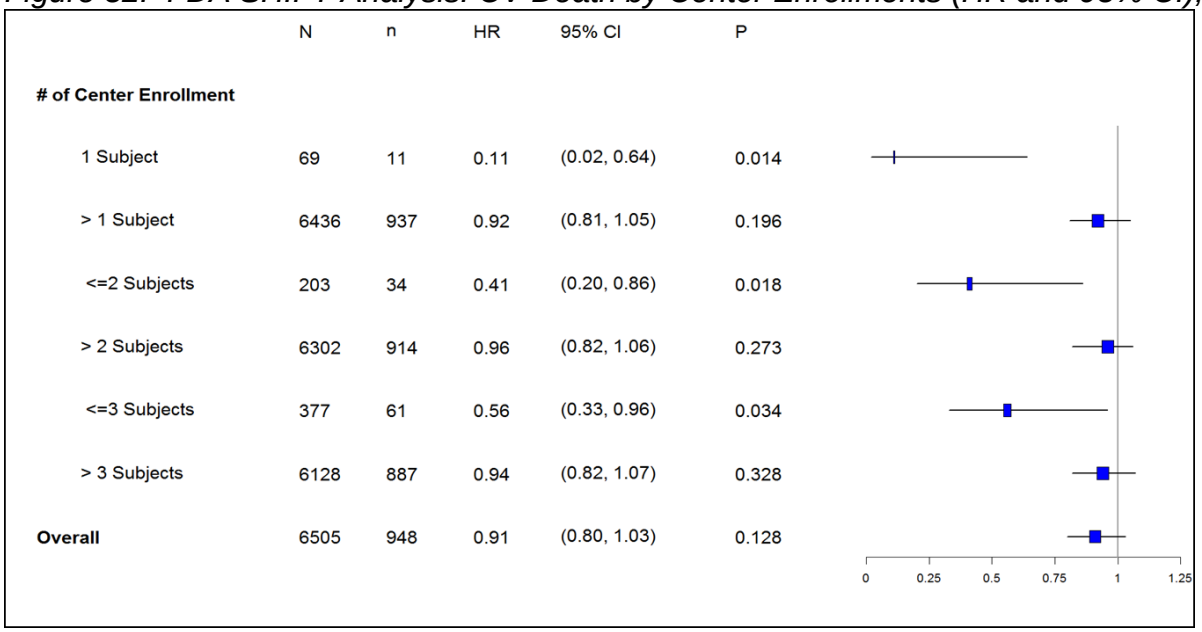
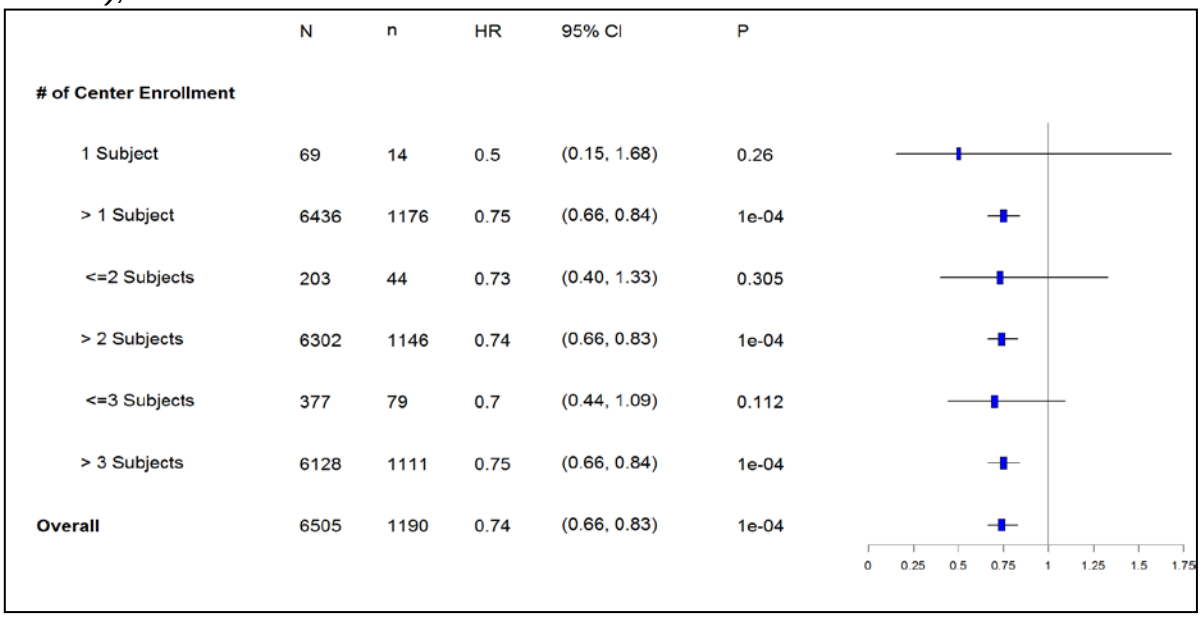


Figure 52. FDA SHIFT Analysis: CV Death by Center Enrollments (HR and 95% CI), RS



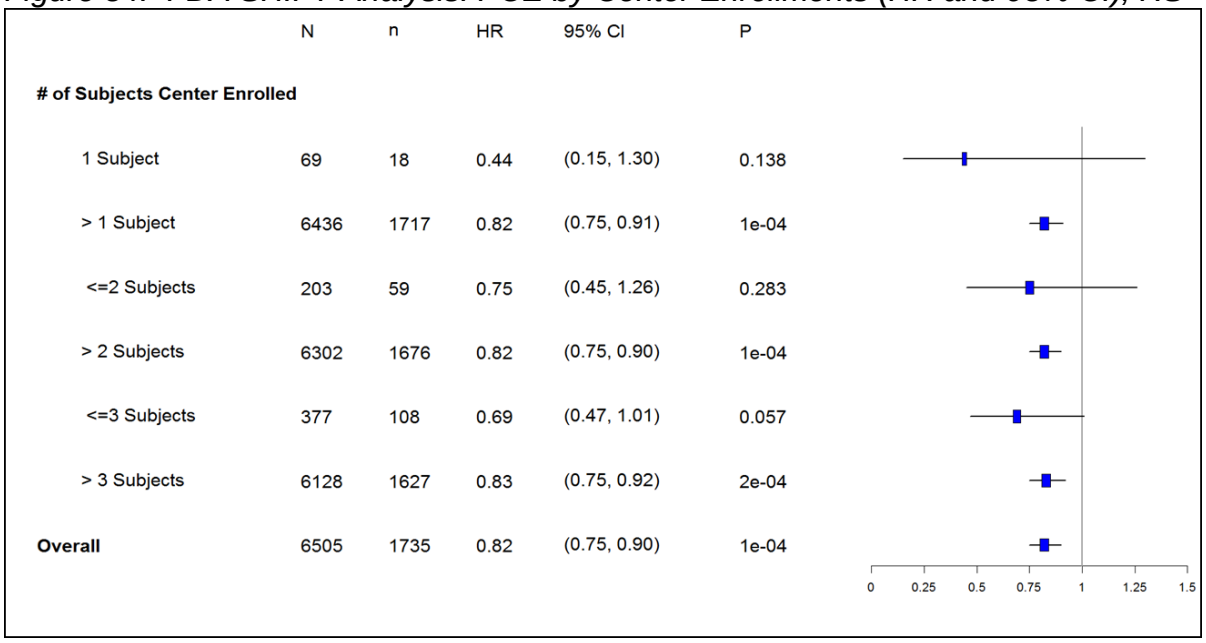
This trend was much less noticeable for hospitalizations for WHF at low enrolling centers, as seen in Figure 52 below:

Figure 53. FDA SHIFT Analysis: Hospitalizations for WHF by Center Enrollments (HR and 95% CI), RS



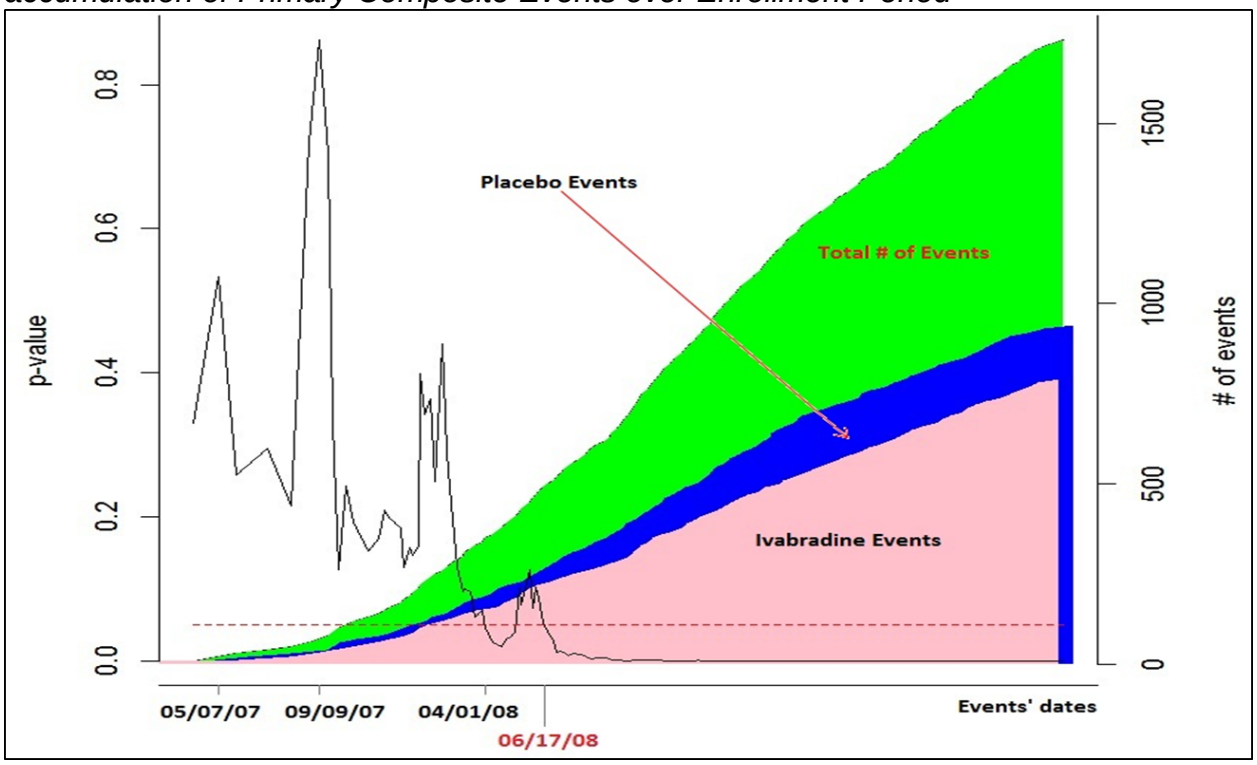
As expected, the PCE forest plot for the low enrolling centers was a blend of the death and hospitalization curves:

Figure 54. FDA SHIFT Analysis: PCE by Center Enrollments (HR and 95% CI), RS



Because we did not have an encrypted randomization/allocation code submitted in advance (with the encryption key submitted with the NDA so that the Division could verify the accuracy of the allocation of events), a simultaneous assessment of the accumulation of primary outcome events in both treatment arms, together with a display of the ongoing p-value of the primary composite endpoint, was performed to assure that there were no discontinuities that might imply an abrupt allocation switch for reported outcome events. This in fact was not the case, as demonstrated by the smooth and continuous nature of the accumulation of primary endpoint events in both arms, as is seen in Figure 56 below:

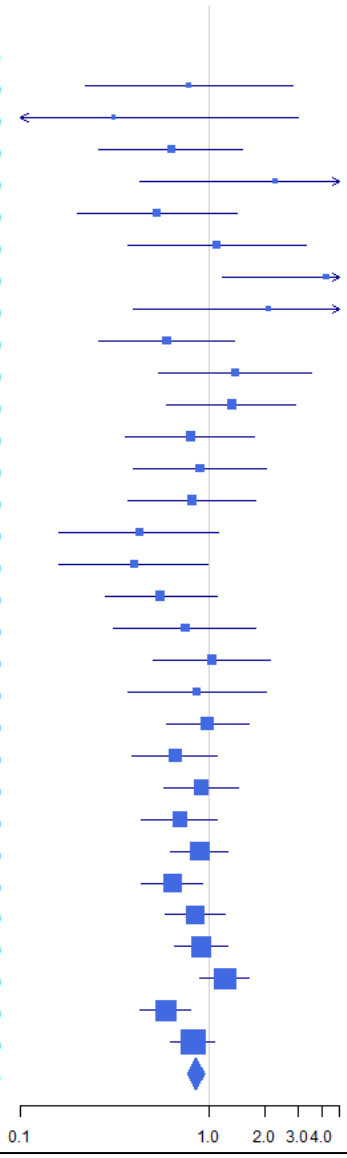
Figure 55. FDA SHIFT Analysis: Distribution of Cox PH model p-values along with accumulation of Primary Composite Events over Enrollment Period



In addition, efficacy outcomes were assessed for each country as a forest plot analysis, with most showing positive results for the PCE, and no obvious outliers, as seen in Figure 57 below:

Figure 56. FDA SHIFT Analysis: Forest Plots of Hazard Ratio and 95% CI for Primary Composite Endpoint Comparing Ivabradine to Placebo by Country

Country	#events/N (Placebo)	#events/N (Ivabradine)	HR	(95% CI)
MALAYSIA	6/12	4/9	0.78	(0.22 , 2.79)
CANADA	3/16	1/14	0.31	(0.03 , 3.01)
PORTUGAL	10/16	11/20	0.63	(0.26 , 1.52)
SLOVENIA	2/20	5/24	2.24	(0.43 , 11.76)
SWEDEN	13/26	6/23	0.53	(0.20 , 1.41)
BELGIUM	6/26	7/26	1.1	(0.37 , 3.30)
GREECE	3/30	12/34	4.24	(1.19 , 15.06)
KOREA, REPUBLIC OF	2/28	5/36	2.07	(0.40 , 10.70)
TURKEY	15/35	9/31	0.6	(0.26 , 1.37)
ESTONIA	8/35	10/33	1.38	(0.54 , 3.51)
CHILE	11/36	15/38	1.32	(0.60 , 2.88)
SLOVAKIA	14/40	11/35	0.8	(0.36 , 1.76)
SPAIN	13/39	11/38	0.9	(0.40 , 2.02)
NETHERLANDS	16/45	10/38	0.81	(0.37 , 1.78)
DENMARK	13/45	6/47	0.43	(0.16 , 1.13)
INDIA	15/47	7/45	0.4	(0.16 , 0.99)
FRANCE	20/51	14/54	0.55	(0.28 , 1.11)
LITHUANIA	12/59	9/52	0.75	(0.31 , 1.78)
ITALY	17/59	14/53	1.04	(0.51 , 2.14)
GERMANY	11/83	10/85	0.86	(0.37 , 2.02)
LATVIA	30/98	31/101	0.98	(0.60 , 1.63)
CZECH REPUBLIC	36/121	24/116	0.66	(0.39 , 1.11)
BRAZIL	36/119	38/127	0.91	(0.58 , 1.43)
CHINA	43/171	30/170	0.7	(0.44 , 1.11)
HUNGARY	66/195	58/192	0.9	(0.63 , 1.27)
ARGENTINA	67/203	47/211	0.64	(0.44 , 0.92)
POLAND	62/241	54/239	0.85	(0.59 , 1.23)
BULGARIA	76/278	69/275	0.91	(0.66 , 1.27)
ROMANIA	77/329	91/322	1.22	(0.90 , 1.65)
UKRAINE	104/355	67/355	0.59	(0.43 , 0.80)
RUSSIAN FEDERATION	120/367	101/361	0.82	(0.63 , 1.07)
No U.R.*	**713/2542**	**625/2525**	**0.86**	**(0.77 , 0.95)**



7 Review of Safety

Safety Summary

The rationale for the development of ivabradine for heart failure was based on observational studies that suggested an increase in mortality and cardiovascular risk with increasing HR > 70 bpm. Ivabradine inhibits the f-current (I_f), which plays a role during spontaneous diastolic depolarization, thereby increasing the time required to reach the voltage threshold for action potential initiation and slowing the spontaneous firing of sino-atrial node cells. Because ivabradine reduces the rate of pacemaker activity in the sinoatrial node, it reduces the heart rate. The applicant asserts that the effects are specific to the sinus node, without negative effects on myocardial contractility or ventricular repolarization.

Ivabradine and its major metabolite are equipotent, and both are extensively metabolized by CYP3A4. Both are substrates of p-glycoprotein (p-gp). Ivabradine also inhibits p-gp with an IC_{50} of 72 µM, the approximate concentration expected to be achieved with a 7.5 mg dose in the gut.[7] Ivabradine does not appear to inhibit OCT2. Primarily because of first pass metabolism, the absolute bioavailability is only ~40%. Ivabradine is minimally excreted unchanged. Metabolites are excreted equally in urine and feces.

The pharmacodynamics of ivabradine include 1) dose dependent heart rate reduction (HRR) at rest and at exercise, 2) a plateau effect, whereby the incremental HRR is smaller with doses above (b) (4) mg BID, and 3) HRR that is proportional to the baseline HR. That is, ivabradine reduces HR more at higher HRs, and inversely, ivabradine reduces HR less at lower HRs. In dose finding studies ivabradine 2.5 mg BID, 5 mg BID, and 7.5 mg BID reduced HR by ~ 10-11 bpm. Doses higher than 10 mg BID were associated with phosphenes, a phenomenon characterized by seeing light without light actually entering the eye.[8] Thus, the applicant continued with doses less than 10 mg BID into Phase 3.

The safety review focuses on the Phase 3 trial submitted for registration in heart failure, SHIFT. Supportive safety information came from BEAUTIFUL, also a Phase 3 trial but in a different population than SHIFT.[9] Because of differences in study population, the applicant identified post-hoc two sub-populations in BEAUTIFUL that were "SHIFT-like" for efficacy analyses, primarily a population with a baseline HR≥ 70 bpm and NYHA Class II/III heart failure.[10] The safety reviewer did not conduct analyses on such a sub-population in her

[7] The major metabolite appears to have a very small capacity to inhibit p-glycoprotein. However, a dedicated drug interaction study with digoxin, a p-gp substrate showed no changes in PK.
[8] The cardiac current I_f is carried by hyperpolarization-activated, cyclic nucleotide-gated channels (HCN), a family of 4 homologous transmembrane proteins that are expressed in the sinoatrial node, AV node, brain, and retina.
[9] The datasets for the Phase 3 trial, SIGNIFY, were submitted at the end of October. Because of the timing of the submission and different patient population, the reviewer did very little of her own analyses of the SIGNIFY data.
[10] SHIFT median HR 77 bpm, ivabradine arm NYHA Class II (48.9%), NYHA Class III (49.5%)

safety review since she considered the data in SHIFT adequate to summarize the safety of ivabradine in heart failure. In addition, BEAUTIFUL had a placebo-control, so treatment effect was evaluable, and her preference was to conduct the safety analysis on the entire randomized population in BEAUTIFUL.

Out of 6,558 randomized subjects in SHIFT, 6,538 subjects were treated (3260 with ivabradine, 3278 with placebo). The treatment duration in SHIFT was ~20 ± 9 months in each arm and total study duration was ~ 22 ± 8 months (mean ± SD). In SHIFT ~60% of subjects took 5 mg BID up-titrated to 7.5 mg BID.

BEAUTIFUL included ~ 66% more subjects than SHIFT; the treatment duration was ~3 months less and study duration ~2.5 months less than SHIFT. In BEAUTIFUL most subjects remained on 5 mg BID; only 40% of subjects took 5 mg BID up-titrated to 7.5 mg BID. This is likely because BEAUTIFUL criteria for entry included a 10 bpm lower baseline HR then SHIFT, yet had similar titration rules (**Table 50**). A notable difference in titration was the unavailability of a 2.5 mg dose in BEAUTIFUL. This likely contributed to the greater discontinuations for asymptomatic bradycardia (the applicant termed "HR decreased") in BEAUTIFUL compared to SHIFT. The applicant called symptomatic bradycardia "bradycardia". Another difference was that investigators were not allowed up-titrate after the Day 15 visit in BEAUTIFUL.

Table 50. Guidelines for dose titration – SHIFT & BEAUTIFUL

	SHIFT	**BEAUTIFUL**
Baseline inclusion HR on 12-lead ECG	**≥ 70 bpm**	**≥ 60 bpm**
Visit Day 14 HR on resting ECG[1]	**Dose to continue**	**Dose to continue**
> 60 bpm[1]	7.5 mg BID	7.5 mg BID
50 – 60 bpm	5 mg BID	5 mg BID
< 50 bpm or signs, symptoms likely due to bradycardia	2.5 mg BID	Treatment discontinued
Visit Day 28 HR on resting ECG and subsequent visits		
≥ 50 bpm	Maintain previous dose	If 7.5 mg maintain dose If 5 mg and no symptoms, maintain dose
≥ 60 bpm & taking 2.5 mg or 5 mg BID	Increase to next dose	Not applicable
< 50 bpm or symptoms likely due to bradycardia & taking 5 mg or 7.5 mg BID	Decrease to next lower dose	If 7.5 mg, reduce to 5 mg If 5 mg, discontinue drug
< 50 bpm or symptoms likely due to bradycardia & taking 2.5 mg	Stop the treatment	Not applicable

Starting dosage was 5 mg BID in both trials

1. BEAUTIFUL- Visit Day 15, criteria was HR ≥ 60 bpm. In BEAUTIFUL up-titrations were not allowed after the D15 visit. SHIFT allowed up-titrations.

Deaths

Since death was an adjudicated endpoint and cardiovascular death was part of the primary composite efficacy endpoint, most of the discussion about death is in the Efficacy section. In SHIFT there were a total of 1075 deaths during the trial in treated subjects, 512 (8.6%PY) in subjects treated with ivabradine and 563 (9.5%PY) in subjects treated with placebo. The applicant reports 1074 because they only reported deaths for randomized

subjects. (One subject was treated, but was never randomized.) The largest type of death was "sudden death and sudden cardiac death", 3.7%PY in ivabradine treated subjects and 4.1%PY in placebo treated subjects. "Heart failure NEC" was 2.1%PY and 2.5%PY in the ivabradine and placebo treated subjects, respectively. Death from ventricular fibrillation was almost 3 fold higher with ivabradine compared to placebo.

Serious Adverse Events

The total number of subjects with an SAE in SHIFT was 1371 (42.1%) ivabradine treated subjects and 1479 (45.1%) placebo treated subjects. In BEAUTIFUL there were fewer subjects with SAEs, but like SHIFT, placebo treated subjects had more SAEs compared to ivabradine treated subjects.

SAEs with ≥ 2x risk in ivabradine treated subjects compared to placebo treated subjects included bradycardia (~7.5x higher, 0.3%PY), conduction disturbances (~2.3x higher, and including complete or third degree AV block, and sinus arrest), and sick sinus syndrome (5 ivabradine subjects vs. 0 placebo subjects).[11] These events are consistent with the mechanism of action of ivabradine and location of HCN4.

Other SAEs that occurred more frequently in ivabradine treated subjects include arrhythmias (most notably atrial fibrillation (20% higher), ventricular fibrillation (83% higher), tachycardia (13% higher) and PVCs (68% higher)), acute renal failure (72% higher), and hypertension/increased BP (24% higher).

Treatment Discontinuations

The rate of drug withdrawal, which includes permanent discontinuation and withdrawal with no restart date, was 8.7%PY and 7.6%PY (ivabradine vs. placebo) in SHIFT.[12] The top reasons for ivabradine withdrawal in SHIFT were atrial fibrillation, HR decreased, and bradycardia. The withdrawal of ivabradine because of permanent atrial fibrillation was protocol driven. Ivabradine withdrawals for asymptomatic bradycardia in BEAUTIFUL were 7.5%PY (compared to 0.5%PY in SHIFT). The threshold to stop ivabradine was lower in BEAUTIFUL compared to SHIFT (there was no 2.5 mg dose in BEAUTIFUL). Subjects were also seen more frequently and there was no up-titration allowed after the D15 visit in BEAUTIFUL. It is unclear if this practice is why the rates of ivabradine related adverse events were less in BEAUTIFUL compared to SHIFT. In BEAUTIFUL there was less vertigo vestibular dysfunction, asthenia, fatigue, weakness, conduction disturbance, ventricular fibrillation, less sick sinus syndrome, and no torsade (whereas SHIFT had 2 cases in the ivabradine treated subjects) compared to SHIFT.

[11] For most subjects bradycardia occurred within the first 6 months of treatment. Bradycardia is also discussed in **Section 7.3**.

[12] The rate of permanent drug discontinuation was 5.8%PY and 4.7%PY (ivabradine vs. placebo) in SHIFT.

Common adverse events
The most common adverse event was arrhythmias (14.9%PY vs. 11.1 %PY, ivabradine vs. placebo, RR 1.33). These included atrial fibrillation, ventricular arrhythmias, bradycardia, and PVCs. The time to first symptomatic bradycardia occurred early in SHIFT (steep rise in first month), and it continued to rise throughout the trial (**Figure 58**). Please see **Section 7.3.5.1** for a thorough discussion of bradycardia. Another common adverse event was conduction disturbance, which consisted mostly of AV block.

Phosphenes were a common adverse event with a high relative risk compared to placebo (5-fold), and a reason for drug discontinuation in 0.2% of ivabradine treated subjects. It was rarely severe or serious. The applicant conducted a 3 year study to evaluate if ivabradine causes retinal degeneration. Although the trial is still blinded, the ophthalmic safety committee has so far concluded that the data to date (~75% completed the trial) has raised no concerns.

Table 51 shows other common adverse events occurring in at least 2% of ivabradine treated subjects and/or the lower 95% CI was greater than 1. Some adverse events are listed to show the components of the adverse event term.

Table 51. Adverse events occurring in ≥ 2 % of ivabradine treated subjects with lower 95% CI >1

	SHIFT					
	Ivabradine N=3260		Placebo N=3278			
Adverse events	%	%PY	%	%PY	RR	(95% CI)
Arrhythmia	(24.7)	14.9	(18.6)	11.1	1.33	(1.21, 1.46)
Atrial fibrillation	(8.2)	4.9	(6.6)	3.9	1.25	(1.05, 1.49)
Bradycardia	(4.5)	2.7	(0.9)	0.5	5.31	(3.56, 7.93)
Ventricular arrhythmia	(6.9)	4.1	(6.6)	3.9	1.04	(0.87, 1.25)
PVCs (ventricular extra systoles)	(4.4)	2.7	(4.2)	2.5	1.05	(0.84, 1.32)
Hypertension, BP increased	(8.7)	5.2	(7.7)	4.6	1.13	(0.96, 1.33)
HR decreased	(5.6)	3.3	(1.4)	0.8	4.04	(2.93, 5.58)
Conduction disturbance	(3.3)	2.0	(2.8)	1.7	1.17	(0.89, 1.54)
AV block	(1.9)	1.1	(1.6)	0.9	1.18	(0.82, 1.70)
Phosphenes, visual brightness	(2.8)	1.7	(0.5)	0.3	5.08	(3.07, 8.40)
Asthenia, fatigue, malaise, weakness, narcolepsy	(1.8)	1.1	(1.2)	0.7	1.59	(1.06, 2.38)

Reviewer's analysis, adapted from Table 68.

Atrial fibrillation
Atrial fibrillation was one of the most common adverse events, SAE, reason for drug discontinuation, and adverse event requiring added therapy where the rates were higher in ivabradine treated subjects compared to placebo treated subjects (see **Table 68**). There is a clear separation of atrial fibrillation/flutter between ivabradine and placebo treated subjects (see **Figure 60, Figure 61, Figure 62**). The onset of separation, however, differs between the three Phase 3 trials; SIGNIFY ~1-2 months, SHIFT ~6 months, and BEAUTIFUL ~ 12 months. The reason for the difference is unclear. Despite occurring in

more than 8% of the ivabradine treated subjects in SHIFT, the sample size is too small to make any conclusions about risk of stroke from ivabradine.

Acute renal failure
The incidence of serious ARF is higher in subjects treated with ivabradine compared to placebo in SHIFT and BEAUTIFUL, with a risk of ~60-70% in SHIFT and ~3.5x greater in BEAUTIFUL. The number of subjects affected was low (0.4% vs. 0.2% of ivabradine treated subjects vs. placebo in SHIFT). Subjects with serum creatinine increased in SHIFT were 1.7% vs. 1.4% (ivabradine vs. placebo), for a RR of 1.22. There were also more discontinuations for acute renal failure in ivabradine treated subjects. (See **Table 70** and **Table 71.**) The data from SIGNIFY suggests that ARF is not a concern with ivabradine, but chronic renal failure might be. Subjects in SIGNIFY had better EFs (mean 56%, compared to 29% in SHIFT and 34% in BEAUTIFUL). This raises the question of whether subjects with heart failure are at risk for renal failure from ivabradine because their cardiac output is more dependent on heart rate given their reduced stroke volumes. Another question raised was whether these cases were actually ARF on top of chronic renal failure (as opposed to ARF in patients with normal renal function). The cases of renal failure will be examined more closely.

Special populations
Severe renal impairment did not affect unbound ivabradine concentrations. The impact of renal failure on the PK of ivabradine and its metabolite were minimal, which is consistent with the low contribution of renal clearance to the overall elimination of ivabradine and its metabolite. In subjects with mild or moderate hepatic impairment, a slight increase in total, but not unbound ivabradine concentrations was observed. The differences in PK did not result in a difference in HRR in subjects with hepatic impairment compared to subjects with normal hepatic function.

Drug interactions
The applicant contraindicates its use with strong CYP3A4 inhibitors. These drugs and grapefruit juice were excluded from their Phase 3 trials. Drugs that prolong the QT interval were “not recommended”. Drugs that may cause excessive bradycardia, such as amiodarone and beta-blockers were allowed with the stipulation that study drug might have to be decreased or withdrawn. A 12-lead ECG was to be obtained 2 weeks after starting a beta-blocker and 2 weeks after each dose increment.
.

Reviewer’s overall safety conclusion
Ivabradine is an I_f channel blocker, whose adverse event profile is generally consistent with the location of HCN expression (the SA node, AV node, retina, and brain). The primary adverse events include bradycardia/HRR, atrial fibrillation, ventricular arrhythmias, sick sinus syndrome, AV block, and phosphenes. At the time of finalization of this review, ivabradine also appears to cause acute renal failure in subjects with symptomatic heart failure. This will be examined in more detail prior to the Advisory Committee meeting.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary sources of data for safety were the Phase 3 trials, SHIFT and BEAUTIFUL. The reviewer analyzed data from both trials, but gave more emphasis to SHIFT since it was conducted in the proposed population. SIGNIFY was conducted in 19,102 patients with stable CAD without symptomatic heart failure (mean EF 56%). Because of the different population compared to SHIFT, and the relatively late timing of the SIGNIFY data during the review cycle, the safety reviewer did very little of her own analysis of the SIGNIFY data.[13] (See **Table 29** for a comparison of the three Phase 3 trials.)

The next table shows the balanced number of subjects and patient years (between treatment arms) for various analysis populations in the three Phase 3 trials. In total, the applicant excluded 27 subjects randomized to ivabradine and 26 subjects randomized to placebo from the SHIFT randomized set because of misconduct or not meeting inclusion criteria.[14]

The reviewer's safety analysis was conducted by treatment and included all subjects who received at least one dose of investigational product. The applicant's safety analysis was conducted by randomized treatment and included all treated subjects except for those subjects at the two sites identified with study misconduct prior to unblinding.

[13] More analyses of important adverse events are planned. If the results change the conclusions of this review, an addendum will be filed.

[14] Note that in addition to the two Polish sites that the applicant excluded from all analyses because of misconduct, the applicant informed us during the review cycle that site 1210 in the Czech Republic also had misconduct, however its data are included in all analysis sets. The decision to exclude the two Polish sites was made prior to database lock and unblinding in 2010. For site 1210, the applicant was unable to gain full access to electronic hospital records until May 2014.

Table 52. Analysis populations in Phase 3 trials

	SHIFT		BEAUTIFUL		SIGNIFY	
Subjects Randomized	N=6,558		N=10,917		N=19,102	
Subjects Treated	N=6,538*		N=10,907		N=19,083	
Population	**Ivabradine**	**Placebo**	**Ivabradine**	**Placebo**	**Ivabradine**	**Placebo**
Randomized	3268	3290	5479	5438	9550	9552
Randomized (applicant's)[1]	3241	3264	5479	5438	9550	9552
Treated (reviewer's safety)	3260	3278	5477	5430	9539	9544
Applicant's safety set[2]	3232	3260	5477	5430	9539	9544
Patient years						
Randomized (applicant)	5954	5917	8510.6	8427.9	21594	21699
Treated (reviewer's safety)	5425.4	5513.2	7239.9	8144.1	19582.7	20685.6
Reviewer's time in study	5971.1	5925.5	8892.9	8828.8	22003.5	22092.3
Applicant's safety set[2]	5401.1	5495.3	7239.9	8144.1	19582.7	20685.6
Applicant's time in study	5942.4	5909.1	8892.9	8828.8	22003.5	22092.3

1. Excludes 53 subjects: 7 subjects (2 ivabradine) that did not meet inclusion criteria (and were never treated), all subjects from Polish sites 1121 (n=23) and 1142 (n=23) for study misconduct.
2. Excludes 46 subjects (25 ivabradine) from Polish site 1121 and 1142. Applicant's number shown is by randomized treatment. Actual treatment in their safety set was 3235 ivabradine, 3257 placebo.

*One subject (ID 278 from Russian site 1441) in the safety population received treatment with placebo but was never randomized in SHIFT.
Reviewer's analysis: BS\data\patient years. Applicant's data: popset

Ivabradine has been approved since 2005 in the EU for angina (and in 2012 for heart failure), so post marketing data and safety update reports were also reviewed. The following special studies were also examined.

1. 24-h Holter ECG study (a SHIFT sub study) which included the analysis of heart rate variability at baseline and Month 8 and assessment of cardiac abnormalities over a 24-hour recording periods.
2. Study CL3-16257-067 Evaluated the 3 year ophthalmic safety of ivabradine 2.5, 5, and 7.5 mg BID on top of anti-anginal therapy.

7.1.2 Categorization of Adverse Events

Adverse events in SHIFT were coded to MedDRA version 9.0; those in BEAUTIFUL were coded to MedDRA version 7.0[15]; those in SIGNIFY were coded to MedDRA version 16.0. The reviewer analyzed the adverse event data three different ways for SHIFT and BEAUTIFUL:

1. MedDRA terms by assigned treatment using the applicant's safety population. The reviewer did this to confirm the applicant's method of analysis.
2. MedDRA terms by treatment received using the reviewer's safety population.[16]
3. Grouping related preferred terms into an "adverse event", and then analyzing by treatment received using the reviewer's safety population.

[15] The applicant also provided terms coded to version 9.0 in the adverse event dataset (ADVEN)
[16] This was done with MAED (FDA's MedDRA Based Adverse Event Diagnostics software used for analyzing MedDRA coded data) and with SAS.

Reviewer comment: A combination of analysis #2 and #3 are shown in the main tables of the safety review. Results from each analysis (#2 and #3) can be found in the Appendix. Results from analysis #1 (applicant's analysis method) were similar to #2, but are not included in the review. The difference in some counts between analysis #1 and #2 are because three subjects randomized to placebo actually received ivabradine and one subject not randomized was treated with placebo. Also, the reviewer included all subjects treated whereas the applicant excluded subjects from 2 Polish sites. These reasons account for the differences between the sponsor's analysis (#1) and analysis #2.

In addition, for the SAE analysis, the applicant includes fatal SAEs, whereas the reviewer does not since fatal adverse events are discussed in **Section 7.3.1 Deaths***. For BEAUTIFUL the applicant removed SAE that were related to coronary artery disease and left ventricular dysfunction (such as cardiac failure, unstable angina) from their SAE tables in the CSR. The reviewer did not. It is reasonable to consider those SAEs separately since some were related to the efficacy endpoint and were adjudicated.*

The reviewer performed Analysis #3 because some preferred terms (PT) in SHIFT should have been grouped together. A prominent example includes the treatment emergent PT's "Acute myocardial infarction" (AMI) and "myocardial infarction". "Myocardial infarctions" were AMIs, so these terms were grouped together. The next table shows some of the groupings used for adverse events that appear in the main tables in this review. Tables with column headings of "adverse events" include reviewer grouped terms. Adverse events that are preferred terms are highlighted in red font.

The applicant used the term "HR decreased" to describe an asymptomatic reduction in HR, and "bradycardia" to describe a symptomatic reduction in HR. Thus, the definition of "bradycardia" used in the applicant's adverse event analysis was not based on a specific HR.[17] *The reviewer found that the use of these terms as the applicant defined them was consistent. For example, asymptomatic sinus bradycardia was coded to "HR decreased". The reviewer also shows results for the two terms combined.*

[17] AHA defines bradycardia as a HR < 60 bpm, irrespective of symptoms

Table 53. Reviewer's grouped adverse events and included preferred terms that appear in adverse event tables (Section 7.4.1)

Reviewer adverse event name	Included preferred terms[1]
Acute MI	myocardial infarction, acute myocardial infarction
Bradycardia, heart rate decreased	Bradyarrhythmia, heart rate decreased, sinus bradycardia
Conduction disturbance	Sinoatrial block, Sinus arrest, trifascicular block, AV block, BBB, QRS prolonged
Hypertension, BP increased	Hypertension, BP increased, BP inadequately controlled
Phosphenes	Phosphenes, visual brightness
Pneumonia	Pneumonia, pneumonia aspiration, pneumonia klebsiella, pneumonia pneumococcal, pneumonia primary atypical
Supraventricular	Supraventricular tachycardia, atrial tachycardia, atrial fibrillation
Syncope	Syncope vasovagal, loss of consciousness, drop attacks
Transaminases abnormal	Liver function test abnormal, ALT abnormal, hepatic function abnormal, hepatic enzyme increased, ALT increased
Visual disturbance, corneal deposits	Vision blurred, cyanopsia, erythropsia, visual acuity reduced

1. Not a complete list of included preferred terms

Most analyses presented in the review were on treatment defined as from first dose of study drug to last dose plus 2 days, unless otherwise stated. The reviewer also analyzed adverse events during the entire trial period and compared the results to the on treatment results.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The applicant did not pool the data from the Phase 3 trials. The MedDRA datasets were not pooled because of different MedDRA versions. For the grouped analysis #3, adverse events were pooled, but because of differences in study population, the reviewer presents the results by trial.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and 7.2.2 Explorations for Dose Response

Dose Exploration

The rationale for the development of ivabradine for heart failure was based on observational studies that suggested an increase in mortality and cardiovascular risk with increasing HR > 70 bpm. Ivabradine reduces the rate of pacemaker activity in the sino-atrial node and thereby lowers heart rate. Ivabradine inhibits the f-current (I_f), which plays a role during spontaneous diastolic depolarization, thereby increasing the time required to reach the voltage threshold for action potential initiation and slowing the spontaneous firing of sino-atrial node cells. The applicant claims that the effects are specific to the sinus node, without negative effects on myocardial contractility or ventricular repolarization.

Phase 1 trials evaluated single or multiple oral doses ranging from 0.5 to 40 mg and single IV doses (bolus or infusion over 48 hours) ranging from 1 to 80 mg. Doses of ≥ 28 mg maintained HRR 24 hours post dose. The data suggested that twice daily administration was necessary to maintain HRR over a 24 hour period. Twice daily dosing was also supported by the PK (effective half-life 11 hours per the applicant). Doses of ≥ 10 mg were associated with phosphenes and visual symptoms, sometimes lasting for 3 days.

The applicant's PK/PD analysis of pooled data from CAD and chronic stable angina patients found the following: 1) dose dependent (2.5 mg to 20 mg BID) heart-rate lowering at rest and at exercise, 2) "plateau effect" – the incremental HRR was smaller with doses above 10 mg BID, and 3) HRR is proportional to the baseline heart rate. This is in line with ivabradine mechanism of action. Ivabradine inhibits I_f in a concentration dependent manner. Inhibition requires ivabradine molecules from the intracellular side of the membrane to enter the HCN4 channel pore while it is in its open conformation. This requirement for open channels results in "use dependence". That is, a greater ability to reduce HR at higher HRs, and inversely, there is less ability to reduce HR at lower HRs.

The Phase 2 chronic heart failure study, CL2-062 (or NP26408), evaluated 2.5 mg BID x 2 weeks, then 5 mg BID x 2 weeks, then 7.5 mg BID x 2 weeks; at each titration step, subjects with HR < 50 bpm or with signs or symptoms of intolerance remained at the preceding dose. With this regimen, the subjects that completed the study on 2.5 mg BID, 5 mg BID, and 7.5 mg BID were 17%, 17% and 66%, respectively. After 6 weeks, the mean HRR was 10-11 bpm in each dose group. Thus, these three doses continued into Phase 3.

Exposure

SHIFT and BEAUTIFUL were Phase 3 event driven trials. Exposure and treatment duration were adequate. The mean treatment duration in SHIFT was ~20 ± 9 months in each arm and study duration was ~ 22 ± 8 months.[18] The mean treatment duration in BEAUTIFUL was ~15.8 ± 9 months and 17.9 ± 7.3 months (ivabradine and placebo arm, respectively) and study duration was ~ 19.5 ± 6 months. The patient years of exposure were shown in **Table 52**. **Table 54** shows that in SHIFT most subjects were up titrated to 7.5 mg BID and were maintained on that dose during the study. Some subjects were unable to tolerate the 7.5 mg dose and were down titrated. Most subjects in BEAUTIFUL remained on 5 mg BID (**Table 55**). This was likely due to the 10 bpm lower baseline inclusion HR (≥ 60 bpm) in BEAUTIFUL (with similar dose titration based on HR and or symptoms in both trials) compared to SHIFT (inclusion HR ≥ 70 bpm).

[18] These are described for the sponsor's randomized set. Follow-up was end of study date-randomization date +1. The end of study date was defined as the date of death if died during the study or date of last visit/contact.

Table 54. Description dose titration in SHIFT (randomized set)

Sequence of study drug dose administered		Ivabradine (N = 3241)	Placebo (N = 3264)	All (N = 6505)
5 mg	n (%)	282 (8.7)	117 (3.6)	399 (6.1)
5 mg then 7.5 mg	n (%)	1954 (60.3)	2956 (90.6)	4910 (75.5)
5 mg then 7.5 mg then 5 mg	n (%)	225 (6.9)	58 (1.8)	283 (4.4)
5 mg then 2.5 mg	n (%)	233 (7.2)	24 (0.7)	257 (4.0)
5 mg then 2.5 mg then 5 mg	n (%)	94 (2.9)	6 (0.2)	100 (1.5)
Other profile *	n (%)	444 (13.7)	98 (3.0)	542 (8.3)
No study drug taken**	n (%)	9 (0.3)	5 (0.2)	14 (0.2)

N: Total number of patients in the considered treatment group
n: Number of patients concerned
% = (n/N) × 100
** 27 other profiles were described, mainly including 5mg/7.5mg/5mg/7.5mg (6.0% in the ivabradine group versus 1.7% in the placebo group), 5mg/2.5mg/5mg/7.5mg (2.0% versus 0.4%) and 5mg/7.5mg/5mg/2.5mg (1.7% versus 0.4%).*
*** patients excluded from safety analysis*

Source: SHIFT CSR, Table (10.5.3)1

Table 55. Description dose titration in BEAUTIFUL (randomized set)

Sequence of study drug dose administered	Ivabradine (N = 5479)		Placebo (N = 5438)		All (N = 10 917)	
	n	%	n	%	n	%
5 mg	2921	53.3	1241	22.8	4162	38.1
5 mg then 7.5 mg	2207	40.3	4067	74.8	6274	57.5
5 mg then 7.5 mg then 5 mg	348	6.4	120	2.2	468	4.3
Other profile*	1	< 0.1	2	< 0.1	3	< 0.1
No study drug taken**	2	< 0.1	8	0.2	10	0.1

N: Total number of patients in the considered treatment group
n: Number of patients concerned
% = (n/N) × 100
** 5 mg then 7.5 mg then 5 mg then 7.5 mg*
*** excluded from safety analysis*

Source: BEAUTIFUL CSR, Table (10.5.3)1

7.2.3 Special Animal and/or In Vitro Testing

According to the draft FDA pharmacology/toxicology review, the preclinical program was adequate. Pharmacology safety studies, metabolite/PK studies, reproductive studies, QT studies, genotoxicity, and carcinogenicity studies were all done.

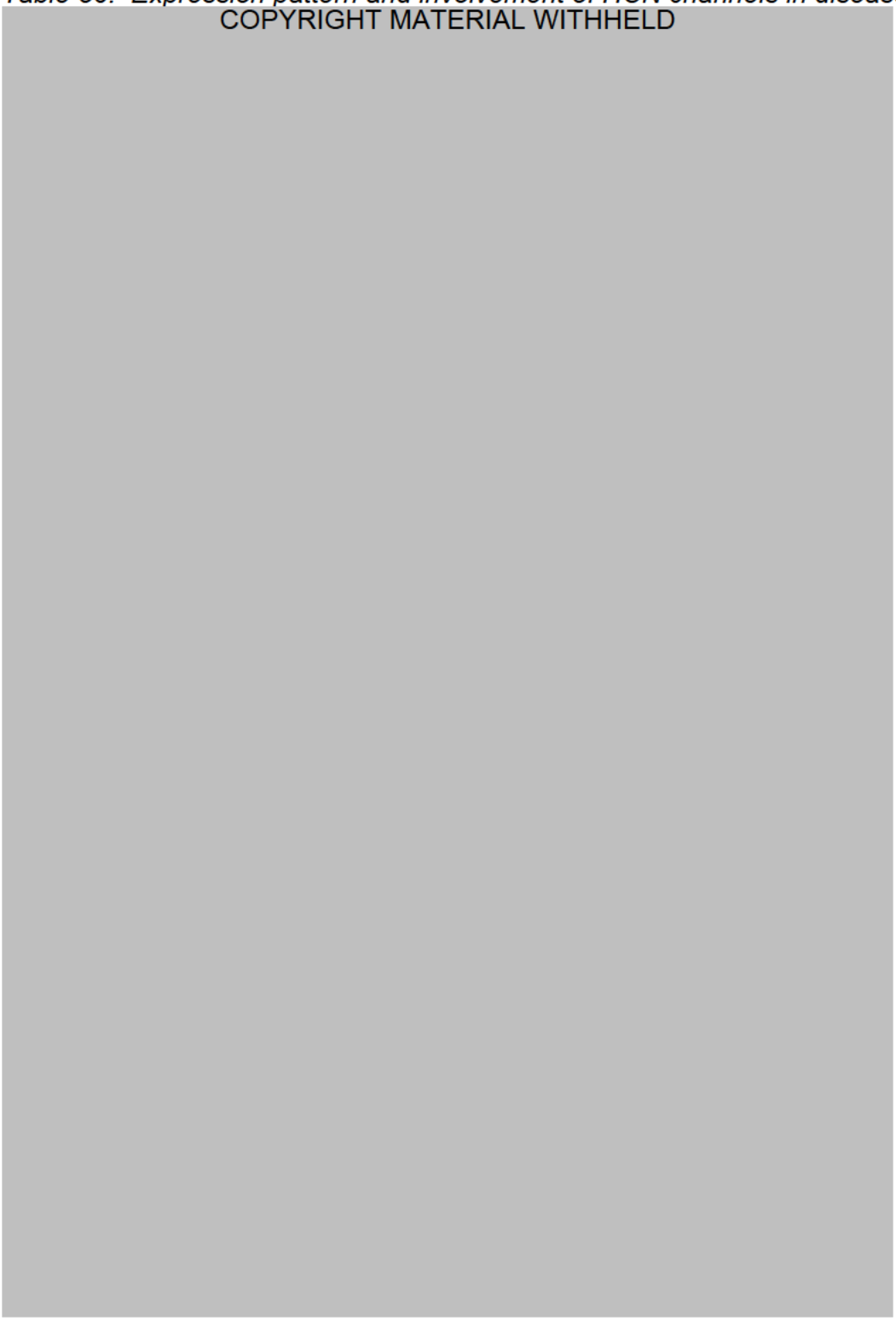
The next table from Nature Reviews Drug Discovery 10, 903-914 (December 2011) shows the expression pattern and involvement of HCN channels in disease. The HCN1 isoform is expressed in retinal photoreceptors and bipolar cells.[19, 20] The table lends some

[19] Muller, F. *et al.* HCN channels are expressed differentially in retinal bipolar cells and concentrated at synaptic terminals.

insight into the adverse event profile of ivabradine. Ivabradine does not appear to selectively target specific HCN channel subtypes.[21,22]

[20] Barrow, A. J. & Wu, S. M. Low-conductance HCN1 ion channels augment the frequency response of rod and cone photoreceptors. *J. Neurosci.* **29**, 5841–5853 (2009).
[21] Melchiorre, M. *et al.* Design, synthesis, and preliminary biological evaluation of new isoform-selective f-current blockers. *J. Med. Chem.* **53**, 6773–6777 (2010).
[22] Stieber, J. Ivabradine: pharmacodynamic aspects of its clinical use. *Methods Find. Exp. Clin. Pharmacol.* **30**, 633–641 (2008).

Table 56. Expression pattern and involvement of HCN channels in disease



HCN, hyperpolarization-activated cyclic nucleotide-gated channel.

7.2.4 Routine Clinical Testing

The schedule of investigations for each trial was provided in Section 5. In all 3 trials, a 12-lead ECG, blood pressure, and adverse events were collected at every planned visit. In SHIFT the planned visits were the selection visit, D0, D14, D28, M4, 8, 12, 16, 20, 24, 28, 32, 44, 48, 52, and termination visit. Local laboratory tests were collected at the Selection visit, M4, 12, 24, 36, 48, and termination visit. Local laboratory tests included ALT, AST, hemoglobin, red blood cell count, white blood cell count, platelet count, sodium, potassium, creatinine, ALT, AST, fasting plasma glucose, total and LDL cholesterol. Cholesterol was only collected at the beginning and end of the trial.

In BEAUTIFUL the planned visits were the selection visit, D0, D15, M1, 3, 6, 12, 18, 24, 30, and 36). Tests for sodium, potassium, creatinine, ALAT, and ASAT were collected at every planned visit. Local laboratory tests for hematology, fasting plasma glucose, and cholesterol were collected at the D0, M12, 24, and 26.

In SIGNIFY the planned visits were the selection visit, M0, 1, 2, 3, 6, 12, 18, 24, 30, 36, 42, 48, 54, and the termination visit. Local laboratory tests for hematology, fasting plasma glucose, and cholesterol were collected at the M0, M12, 24, 36, 48, and termination. Tests for sodium, potassium, creatinine, ALAT, and ASAT were collected at M0, 3, 12, 24, 36, 48, and termination.

Reviewer's comment: The collection of adverse events was most frequent in SIGNIFY, so it is likely that SIGNIFY will have the highest percentage of overall adverse events, "HR decreased" adverse events, and drug discontinuations per protocol. However, the dose in SIGNIFY was also higher than the other two trials. Labs were collected far enough apart that it is unlikely one would detect a signal for an acute event (such as acute renal failure); the timing is better for detection of an adverse event that develops over time. An effort was made to monitor for hepatotoxicity, however bilirubin, an important laboratory value was not collected. This complicates the evaluation for drug induced liver injury in the setting of heart failure. Thus, the reviewer relied on the hepatic adverse event reporting.

7.2.5 Metabolic, Clearance, and Interaction Workup

This is summarized in **Section 4.4 Clinical Pharmacology**. Briefly, ivabradine and its main metabolite are equipotent. They are both extensively metabolized by CYP3A4. Largely because of first pass metabolism, the absolute bioavailability is only ~40% after an oral dose. Ivabradine is minimally excreted unchanged. Metabolites are excreted equally in urine and feces. Severe renal impairment did not affect unbound ivabradine concentrations. In subjects with mild or moderate hepatic impairment, a slight increase in total, but not unbound ivabradine concentrations was observed. The effects of severe hepatic impairment have not been studied. There was not a difference in effect on HRR among subjects with severe renal impairment and normal renal function, nor with subjects with mild and moderate hepatic impairment and normal hepatic function. Age, sex, weight, and race do not affect ivabradine exposure. Ivabradine (b) (4) had no effect on metformin, an OCT2 substrate, in humans.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Bradycardia

In addition to HR, details relating to how bradycardia was documented (clinical examination, ECG tracing, Holter recording) and when it was observed (at rest, exercise, during the day or night) were to be recorded.

The applicant distinguished all emergent cases of bradycardia as either asymptomatic bradycardia (termed “HR decreased”) or symptomatic bradycardia (termed “bradycardia”). Since asymptomatic bradycardia was usually detected during exam, the subject was either examined for another event or was at a planned visit. It is likely then that the incidence of asymptomatic bradycardia was underestimated. Although the underestimation might not be so important clinically, asymptomatic bradycardia was a reason for protocol driven drug discontinuation in 0.9% of ivabradine treated subjects in SHIFT, and 10.2% of ivabradine treated subjects in BEAUTIFUL.

Important in the assessment of bradycardia are other drugs that slow heart rate. Many of them (e.g., amiodarone, verapamil, diltiazem) were either excluded or discouraged. However beta-blockers were used because some have a claim in heart failure. If a beta-blocker was not prescribed or if the dose was lower than the ESC recommended target daily dose for carvedilol, bisoprolol, metoprolol succinate, metoprolol tartrate, or nebivolol, the reason was to be documented on a specific eCRF page.

For patients with a pacemaker, a CRT device (biventricular pacemaker) and/or an ICD, the start date of this treatment and the percent of time that the device was controlling the patient at atrial and/or ventricular level and the stimulation threshold in case of pacemaker functionality was recorded. For patients with an ICD, a count was made of shocks experienced and if they were appropriate.

Atrial fibrillation and supraventricular tachyarrhythmia

Atrial fibrillation was likely underreported. These were not atrial fibrillation trials, so ascertainment of atrial fibrillation was through adverse event reporting. The diagnosis was to be documented (where possible) by an ECG recording. There were neither trans-telephonic monitors to detect patients experiencing paroxysmal atrial fibrillation, nor were there frequent 12-lead ECGs recorded. There were few defibrillators and pacemakers in SHIFT (none in BEAUTIFUL because of exclusion criteria).

Phosphenes

The applicant conducted a dedicated 3 year study to evaluate the phosphene adverse events. This is described in **Section 7.4.5 Special Safety Studies/Clinical Trials.**

7.3 Major Safety Results

7.3.1 Deaths

Since death was an adjudicated endpoint and cardiovascular death was part of the primary composite efficacy endpoint, most of the discussion about death is in the Efficacy section, and that section should be used to describe deaths in labelling. Fatal adverse events, both preferred terms (PT) and high level terms (HLT) are discussed here.

In SHIFT there were a total of 1075 deaths during the study, 512 (8.6%PY) in subjects treated with ivabradine and 563 (9.5%PY) in subjects treated with placebo.[23] The top fatal adverse events were cardiovascular. For the high level terms (HLT) "death and sudden death" and "heart failures NEC", deaths were greater in placebo treated subjects compared to ivabradine treated subjects. The HLT terms "ischaemic coronary artery disorders" and "ventricular arrhythmias and cardiac arrest" were greater in ivabradine treated subjects compared to placebo. Fatal ventricular fibrillation was almost 3 fold higher with ivabradine compared to placebo.

Table 57. Fatal High Level adverse event Term in ≥ 3 ivabradine treated subjects during the trial- SHIFT

	Ivabradine (N = 3260) 5971.1 PY			***Placebo (N = 3278) 5925.5 PY***					
High Level Term	***N= 512***	***(%)***	***%PY***	***N= 563***	***(%)***	***%PY***	***RR***	***95% CI***	
Death and sudden death	222	6.81	3.7	241	7.35	4.1	0.93	0.78	1.10
Heart failures NEC	123	3.77	2.1	150	4.58	2.5	0.83	0.65	1.04
Ischaemic coronary artery disorders	57	1.75	1.0	43	1.31	0.7	1.33	0.90	1.97
Central nervous system haemorrhages and cerebrovascular accidents	25	0.77	0.4	31	0.95	0.5	0.81	0.48	1.37
Ventricular arrhythmias and cardiac arrest	13	0.4	0.2	7	0.21	0.1	1.87	0.75	4.67
Lower respiratory tract and lung infections	11	0.34	0.2	9	0.27	0.2	1.23	0.51	2.96
Sepsis, bacteraemia and viraemia	6	0.18	0.1	9	0.27	0.2	0.67	0.24	1.88
Pulmonary oedemas	5	0.15	0.1	4	0.12	0.1	1.26	0.34	4.68
Pulmonary thrombotic and embolic conditions	4	0.12	0.1	9	0.27	0.2	0.45	0.14	1.45
Respiratory tract and pleural neoplasms malignant cell type unspecified NEC	4	0.12	0.1	0	0	0.0	9.05	0.49	168.
Gastrointestinal vascular occlusion and infarction	3	0.09	0.1	2	0.06	0.0	1.51	0.25	9.02

Reviewer's analysis: SHIFT\data\ae\death mead\sum_fatal, sponsor's data ADVEN

[23] The applicant reports 1074 because they only counted randomized subjects. They also report the results by randomized treatment. The reviewer's extra death was in the subject that received placebo, but was never randomized. The number of deaths reported here also differs from the efficacy analysis because some subjects died after their last visit date (9 ivabradine, 12 placebo) and some subjects were included in the efficacy analysis but were not part of their safety analysis (2 ivabradine, 1 placebo).

Table 58. Fatal Preferred Term in ≥ 3 subjects during the trial- SHIFT

	Ivabradine (N = 3260) 5971.1 PY			***Placebo (N = 3278) 5925.5 PY***					
Preferred Term	***N=512***	***(%)***	***%PY***	***N=563***	***(%)***	***%PY***	***RR***	***95% CI***	
Sudden death	128	3.93	2.1	146	4.45	2.5	0.88	0.70	1.11
Cardiac failure	101	3.1	1.7	123	3.75	2.1	0.83	0.64	1.07
Sudden cardiac death	86	2.64	1.4	88	2.68	1.5	0.98	0.73	1.32
Myocardial infarction	30	0.92	0.5	20	0.61	0.3	1.51	0.86	2.65
Acute myocardial infarction	23	0.71	0.4	18	0.55	0.3	1.29	0.70	2.38
Cardiogenic shock	14	0.43	0.2	16	0.49	0.3	0.88	0.43	1.80
Ventricular fibrillation	11	0.34	0.2	4	0.12	0.1	2.77	0.88	8.68
Ischaemic stroke	10	0.31	0.2	12	0.37	0.2	0.84	0.36	1.94
Death	8	0.25	0.1	4	0.12	0.1	2.01	0.61	6.67
Pneumonia	8	0.25	0.1	7	0.21	0.1	1.15	0.42	3.17
Cardiac failure acute	6	0.18	0.1	3	0.09	0.1	2.01	0.50	8.03
Acute pulmonary oedema	5	0.15	0.1	4	0.12	0.1	1.26	0.34	4.68
Cerebrovascular accident	4	0.12	0.1	8	0.24	0.1	0.50	0.15	1.67
Pulmonary embolism	4	0.12	0.1	9	0.27	0.2	0.45	0.14	1.45
Bronchopneumonia	3	0.09	0.1	2	0.06	0.0	1.51	0.25	9.02
Septic shock	3	0.09	0.1	2	0.06	0.0	1.51	0.25	9.02
Acute coronary syndrome	3	0.09	0.1	3	0.09	0.1	1.01	0.20	4.98
Haemorrhagic stroke	3	0.09	0.1	3	0.09	0.1	1.01	0.20	4.98

Reviewer's analysis: SHIFT\data\ae\death mead\sum_fatal, sponsor's data ADVEN

Fatal adverse events in BEAUTIFUL were similar to that in SHIFT, with a few exceptions. There were more cancer deaths in BEAUTIFUL; gastrointestinal neoplasm 14 (0.16%PY) vs 7 (0.08%PY) subjects, ivabradine vs placebo, respectively. There was no imbalance in SHIFT (9 vs 9 subjects with gastrointestinal neoplasm malignant and unspecified).

7.3.2 Nonfatal Serious Adverse Events

The total number of subjects with an SAE (including subjects that had an SAE prior to dying) was 1371 (42.1%) ivabradine treated subjects and 1479 (45.1%) placebo treated subjects. After excluding subjects that died, 1146 (35%) and 1264 (39%) subjects treated with ivabradine and placebo, respectively, experienced a nonfatal SAE in SHIFT.[24] SAEs occurred in fewer subjects in BEAUTIFUL, but the incidence between treatment arms was also greater in placebo treated subjects.

[24] The Appendix contains the **Table of Non-fatal SAE - SHIFT and BEAUTIFUL**, the **Table of SAE (includes fatal) by preferred term (≥ 0.5% of ivabradine treated subjects) – SHIFT on treatment,** and **Table of Nonfatal SAE by Preferred term (ver 9) occurring ≥0.3%PY ivabradine subjects– SHIFT & BEAUTIFUL**.

Table 59 contains SAEs that the reviewer judged important to show, either because of the incidence, the importance, or the relative importance (possibly related to location of HCN in human body) for understanding ivabradine. The table is generally sorted in decreasing order by adverse events occurring in the SHIFT ivabradine arm, except for nested adverse events (shown by indention). The table shows both the reviewer's grouped similar terms (analysis #3) as well as preferred MedDRA terms (analysis#2, shown in red typed font).

SAEs with very high risk in ivabradine treated subjects (and occurring in at least 5 ivabradine treated subjects) compared to placebo include bradycardia (~7.5x higher), conduction disturbances (~2.3x higher, and including complete or third degree AV block, and sinus arrest), and sick sinus syndrome (SSS).[25] The subjects that developed SSS had underlying conditions and /or were taking beta-blockers that could reasonably explain the sinus node disorder. However, BEAUTIFUL had 8 subjects on ivabradine and 2 on placebo that developed SSS. Again all cases had underlying conditions/medications that could explain the disorder. The reviewer believes that all of these events are consistent with the mechanism of action of ivabradine and location of HCN4. I_f channels are functionally expressed in the SA node and AV node. HCN4 is expressed at a lower level in the AV node compared to the SA node.

Other SAEs that occurred more frequently in ivabradine treated subjects (and occurring in at least 5 ivabradine treated subjects) included arrhythmias (most notably atrial fibrillation (20% higher), ventricular fibrillation (83% higher), tachycardia (13% higher) and PVCs (68% higher)), acute MI (13% higher), acute renal failure (72% higher), and hypertension/increased BP (24% higher)).

The BEAUTIFUL adverse event data indicates that the risk of MI is not greater with ivabradine compared to placebo. Hospitalization for MI was a component of the secondary efficacy endpoint. Analysis of that endpoint and of that endpoint in the group with HR ≥ 70 bpm shows that ivabradine is not worse than placebo. See **Table 26**.

There were two cases of torsades de pointes occurring at ~22 months and ~2 months. It is not surprising given the propensity for HR reduction induced by ivabradine. These are discussed in **Section 7.4.5.2**.

Please see **Section 7.3.5.1** for a discussion on bradycardia/HR decreased, **Section 7.3.5.2** for a discussion on atrial fibrillation and stroke, and **Section 7.3.5.3** for a discussion on renal failure.

There are some SAE that appear higher in the ivabradine compared to placebo treated subjects, but the data in BEAUTIFUL are not supportive. The Standardized MedDRA

[25] For most subjects bradycardia occurred within the first 6 months of treatment. Bradycardia is also discussed in **Section 7.3**.

query (SMQ) Pancreatitis / acute pancreatitis suggested an increase risk with ivabradine, but the numbers are small. The data in BEAUTIFUL and SIGNIFY do not corroborate it.

Table 59. Serious adverse events (includes SAEs temporally associated with or preceding death) in SHIFT and BEAUTIFUL

	SHIFT								BEAUTIFUL							
	Ivabradine N=3260			Placebo N=3278					Ivabradine N=5477			Placebo N=5430				
AE	n	%	%PY	n	%	%PY	RR	(95% CI)	n	%	%PY	n	%	%PY	RR	(95% CI)
All	1371	(42.1)	25.3	1479	(45.1)	26.8	0.93	(0.88, 0.98)	1625	(29.7)	22.4	1770	(32.6)	21.7	0.91	(0.86, 0.96)
CHF or pulmonary edema	550	(16.9)	10.1	705	(21.5)	12.8	0.78	(0.71, 0.86)	432	(7.9)	6.0	465	(8.6)	5.7	0.92	(0.81, 1.04)
CHF	540	(16.6)	10.0	689	(21.0)	12.5	0.79	(0.71, 0.87)	432	(7.9)	6.0	465	(8.6)	5.7	0.92	(0.81, 1.04)
Arrhythmia	230	(7.1)	4.2	195	(5.9)	3.5	1.19	(0.99, 1.43)	246	(4.5)	3.4	249	(4.6)	3.1	0.98	(0.83, 1.16)
Supraventricular	151	(4.6)	2.8	130	(4.0)	2.4	1.17	(0.93, 1.47)	161	(2.9)	2.2	166	(3.1)	2.0	0.96	(0.78, 1.19)
AF or AFL	144	(4.4)	2.7	125	(3.8)	2.3	1.16	(0.92, 1.47)	159	(2.9)	2.2	158	(2.9)	1.9	1.00	(0.80, 1.24)
Atrial fibrillation	126	(3.9)	2.3	106	(3.2)	1.9	1.20	(0.93, 1.55)	127	(2.3)	1.8	134	(2.5)	1.6	0.94	(0.74, 1.19)
Atrial flutter	22	(0.7)	0.4	19	(0.6)	0.3	1.16	(0.63, 2.14)	35	(0.6)	0.5	28	(0.5)	0.3	1.24	(0.76, 2.04)
Ventricular arrhythmia	66	(2.0)	1.2	70	(2.1)	1.3	0.95	(0.68, 1.33)	58	(1.1)	0.8	77	(1.4)	0.9	0.75	(0.53, 1.05)
Ventricular tachycardia	31	(1.0)	0.6	46	(1.4)	0.8	0.68	(0.43, 1.07)	28	(0.5)	0.4	53	(1.0)	0.7	0.52	(0.33, 0.82)
Ventricular fibrillation	20	(0.6)	0.4	11	(0.3)	0.2	1.83	(0.88, 3.81)	16	(0.3)	0.2	13	(0.2)	0.2	1.22	(0.59, 2.53)
Sick sinus syndrome	5	(0.2)	0.1	.		.	.	(., .)	8	(0.1)	0.1	2	(0.0)	0.0	3.97	(0.84, 18.69)
Tachycardia	27	(0.8)	0.5	24	(0.7)	0.4	1.13	(0.65, 1.95)	38	(0.7)	0.5	37	(0.7)	0.5	1.02	(0.65, 1.60)
PVCs (ventricular extra systoles)	15	(0.5)	0.3	9	(0.3)	0.2	1.68	(0.74, 3.83)	10	(0.2)	0.1	9	(0.2)	0.1	1.10	(0.45, 2.70)
Bradycardia, HR decreased	18	(0.6)	0.3	2	(0.1)	0.0	9.05	(2.10, 38.9)	29	(0.5)	0.4	6	(0.1)	0.1	4.79	(1.99, 11.53)
Heart rate decreased	3	(0.1)	0.1	-	-	-	-	-	7	(0.1)	0.1	-	-	-	-	-
Bradycardia	15	(0.5)	0.3	2	(0.1)	0.0	7.54	(1.73, 32.9)	22	(0.4)	0.3	6	(0.1)	0.1	3.64	(1.48, 8.97)

	SHIFT								BEAUTIFUL							
	Ivabradine N=3260			Placebo N=3278					Ivabradine N=5477			Placebo N=5430				
AE	n	%	%PY	n	%	%PY	RR (95% CI)		n	%	%PY	n	%	%PY	RR (95% CI)	
Syncope	14	(0.4)	0.3	24	(0.7)	0.4	0.59	(0.31, 1.14)	21	(0.4)	0.3	27	(0.5)	0.3	0.77	(0.44, 1.36)
Torsade de Pointes	2	(0.1)	0.0	.		.	.	(., .)	.		.	.		.	.	
cardiogenic shock	15	(0.5)	0.3	16	(0.5)	0.3	0.94	(0.47, 1.90)	.		.	7	(0.1)	0.1	.	(., .)
CAD, myocardial ischemia	233	(7.1)	4.3	223	(6.8)	4.0	1.05	(0.88, 1.25)	318	(5.8)	4.4	384	(7.1)	4.7	0.82	(0.71, 0.95)
ACS (AMI and unstable angina)	225	(6.9)	4.1	214	(6.5)	3.9	1.06	(0.88, 1.27)	304	(5.6)	4.2	366	(6.7)	4.5	0.82	(0.71, 0.95)
Acute MI	116	(3.6)	2.1	103	(3.1)	1.9	1.13	(0.87, 1.47)	147	(2.7)	2.0	166	(3.1)	2.0	0.88	(0.71, 1.10)
Angina (includes USA, angina pectoris)	160	(4.9)	2.9	171	(5.2)	3.1	0.94	(0.76, 1.16)	187	(3.4)	2.6	258	(4.8)	3.2	0.72	(0.60, 0.87)
Unstable angina	113	(3.5)	2.1	119	(3.6)	2.2	0.95	(0.74, 1.22)	153	(2.8)	2.1	197	(3.6)	2.4	0.77	(0.63, 0.95)
Infection, all	191	(5.9)	3.5	212	(6.5)	3.8	0.91	(0.75, 1.10)	190	(3.5)	2.6	193	(3.6)	2.4	0.98	(0.80, 1.19)
pneumonia	83	(2.5)	1.5	79	(2.4)	1.4	1.06	(0.78, 1.44)	83	(1.5)	1.1	79	(1.5)	1.0	1.04	(0.77, 1.41)
Stroke, ICH, TIA	71	(2.2)	1.3	94	(2.9)	1.7	0.76	(0.56, 1.03)	108	(2.0)	1.5	114	(2.1)	1.4	0.94	(0.72, 1.22)
Stroke (ischemic, hemorrhagic)	61	(1.9)	1.1	79	(2.4)	1.4	0.78	(0.56, 1.09)	86	(1.6)	1.2	90	(1.7)	1.1	0.95	(0.71, 1.27)
Ischemic stroke	43	(1.3)	0.8	61	(1.9)	1.1	0.71	(0.48, 1.05)	48	(0.9)	0.7	53	(1.0)	0.7	0.90	(0.61, 1.33)
TIA	11	(0.3)	0.2	12	(0.4)	0.2	0.92	(0.41, 2.08)	18	(0.3)	0.2	26	(0.5)	0.3	0.69	(0.38, 1.26)
Systemic embolism	4	(0.1)	0.1	4	(0.1)	0.1	1.01	(0.25, 4.04)	-	-	-	-	-	-	-	-
solid neoplasia, ALL (benign, malignant, unknown)	64	(2.0)	1.2	60	(1.8)	1.1	1.07	(0.75, 1.52)	95	(1.7)	1.3	110	(2.0)	1.4	0.86	(0.66, 1.13)
cancer (non-squamous cell)	48	(1.5)	0.9	45	(1.4)	0.8	1.07	(0.71, 1.60)	72	(1.3)	1.0	90	(1.7)	1.1	0.79	(0.58, 1.07)

	SHIFT								BEAUTIFUL							
	Ivabradine N=3260			Placebo N=3278					Ivabradine N=5477			Placebo N=5430				
AE	n	%	%PY	n	%	%PY	RR	(95% CI)	n	%	%PY	n	%	%PY	RR	(95% CI)
squamous cell skin cancer	2	(0.1)	0.0	.		.	.	(., .)								
leukemia	2	(0.1)	0.0	.		.	.	(., .)								
COPD, COPD exacerbation	38	(1.2)	0.7	35	(1.1)	0.6	1.09	(0.69, 1.72)	30	(0.5)	0.4	35	(0.6)	0.4	0.85	(0.52, 1.38)
bleeding	39	(1.2)	0.7	37	(1.1)	0.7	1.06	(0.68, 1.66)	28	(0.5)	0.4	31	(0.6)	0.4	0.90	(0.54, 1.50)
elevated BUN or Cr, anuria, ARF, CRF, oliguria	29	(0.9)	0.5	28	(0.9)	0.5	1.04	(0.62, 1.74)	34	(0.6)	0.5	26	(0.5)	0.3	1.30	(0.78, 2.16)
ARF, anuria	12	(0.4)	0.2	7	(0.2)	0.1	1.72	(0.68, 4.36)	14	(0.3)	0.2	5	(0.1)	0.1	2.78	(1.00, 7.71)
diabetes, glucose intolerance, hyperglycemia, HbA1c, glycosuria, insulin resistance	29	(0.9)	0.5	36	(1.1)	0.7	0.81	(0.50, 1.32)	30	(0.5)	0.4	28	(0.5)	0.3	1.06	(0.63, 1.77)
Conduction disturbance	25	(0.8)	0.5	11	(0.3)	0.2	2.29	(1.13, 4.65)	21	(0.4)	0.3	22	(0.4)	0.3	0.95	(0.52, 1.73)
AV block	24	(0.7)	0.4	10	(0.3)	0.2	2.41	(1.15, 5.03)	18	(0.3)	0.2	19	(0.3)	0.2	0.94	(0.49, 1.79)
Complete or third degree AV block	17	(0.5)	0.3	4	(0.1)	0.1	4.27	(1.44, 12.7)	10	(0.2)	0.1	12	(0.2)	0.1	0.83	(0.36, 1.92)
sinus arrest, sinus pause, sinus block	1	(0.0)	0.0	.		.	.	(., .)								
Hypertension, BP increased	26	(0.8)	0.5	21	(0.6)	0.4	1.24	(0.70, 2.20)	28	(0.5)	0.4	23	(0.4)	0.3	1.21	(0.70, 2.10)
stone, renal colic	6	(0.2)	0.1	2	(0.1)	0.0	3.02	(0.61, 14.9)	4	(0.1)	0.1	4	(0.1)	0.0	0.99	(0.25, 3.96)
pancreatitis	9	(0.3)	0.2	7	(0.2)	0.1	1.29	(0.48, 3.46)	5	(0.1)	0.1	4	(0.1)	0.0	1.24	(0.33, 4.62)
retinopathy, retinal disorders	3	(0.1)	0.1	2	(0.1)	0.0	1.51	(0.25, 9.03)	2	(0.0)	0.0	2	(0.0)	0.0	0.99	(0.14, 7.03)
glaucoma	3	(0.1)	0.1	1	(0.0)	0.0	3.02	(0.31, 29.0)	2	(0.0)	0.0	2	(0.0)	0.0	0.99	(0.14, 7.03)
cataract	10	(0.3)	0.2	7	(0.2)	0.1	1.44	(0.55, 3.78)	8	(0.1)	0.1	6	(0.1)	0.1	1.32	(0.46, 3.80)

	SHIFT								BEAUTIFUL							
	Ivabradine N=3260			Placebo N=3278					Ivabradine N=5477			Placebo N=5430				
AE	n	%	%PY	n	%	%PY	RR (95% CI)		n	%	%PY	n	%	%PY	RR (95% CI)	
dementia, cognitive dysfunction	2	(0.1)	0.0	1	(0.0)	0.0	2.01	(0.18, 22.2)	.		.	.		.	.	
seizure	2	(0.1)	0.0	.		.	.	(., .)	1	(0.0)	0.0	2	(0.0)	0.0	0.50	(0.05, 5.51)
allergic RXN, hypersensitivity	2	(0.1)	0.0	.		.	.	(., .)	2	(0.0)	0.0	1	(0.0)	0.0	1.98	(0.18, 21.83)
anaphylactic reaction	1	(0.0)	0.0	.		.	.	(., .)	1	(0.0)	0.0	1	(0.0)	0.0	0.99	(0.06, 15.82)
angioedema, angioneurotic, laryngeal edema	1	(0.0)	0.0	.		.	.	(., .)								
low K	2	(0.1)	0.0	.		.	.	(., .)								
asthenia, fatigue, malaise, weakness, narcolepsy	1	(0.0)	0.0	.		.	.	(., .)								
cranial neuropathy, palsy	1	(0.0)	0.0	.		.	.	(., .)								
cholestatic hepatitis	1	(0.0)	0.0	.		.	.	(., .)								

Red font denotes MedDRA preferred terms. Excludes adverse event terms that mean death.
The reviewer's rates of pneumonia are higher than that reported by the applicant because the reviewer grouped various types of pneumonia into "pneumonia"(see **Table 53**).
Reviewer's analysis: SHIFT\ LD2d\serious\LD2dser_mycat_allSAE, BEAUTIFUL\LD2dser_mycatB_allSAE, bs \create table all. Applicant's data: adven

7.3.3 Dropouts and/or Discontinuations

Subject disposition and reason for study discontinuation are discussed in **Section 6.1.3 Subject Disposition**. This section focusses on study drug discontination because of an adverse event. There were a total of 317 subjects (5.8%PY) treated with ivabradine and 261 subjects (4.7%PY) treated with placebo who permenantly stopped drug because of an adverse event in SHIFT. See **Figure 22** for time to drug discontinutation. Arrhythmias (primarily atrial fibrillation) were the most common reason for drug discontinuation (~5% of ivabradine subjects), and the rate was ~40% higher in ivabradine treated subjects. The rates of discontinaution for bradycardia were ~ 4 fold higher ivabradine treated subjects compared to placebo. Drug discontinuations for conduction disturbances were ~2.5 times greater in ivabradine treated subjects compared to placebo. Ivabradine discontinuations for phosphenes and visual brightness was ~70% higher than placebo.

The applicant also included subjects that temporarily stopped drug in their treatment withdrawal table (12.1.2.3) 4 in the SHIFT CSR. These subjects were noted to temporarily stop drug and never restart treatment. This was usually for reasons of consent withdrawal, death, or temporal proximity to the TERM visit. The applicant reports there were 152 patients (4.7%, 2.8%PY) in the ivabradine group and 153 (4.7%, 2.8%PY) in the placebo group. Combining the two types of treatment withdrawal leads to a discontinuation rate of 8.7%PY in the ivabradine group and 7.6%PY in the placebo group (see **Table 60**). The discontinuation for atrial fibrillation was in accordance with the protocol that directed withdrawal for sustained fibrillation.

Table 60. Top adverse event reason for treatment withdrawal –SHIFT

Preferred term	Ivabradine		Placebo	
	%	%PY	%	%PY
All	14.5	8.7	12.8	7.6
Atrial fibrillation	4.2	2.5	3.5	2.1
Cardiac failure	2	1.2	2.4	1.4
HR decreased	0.9	0.5	0.2	0.1
Bradycardia	0.6	0.4	0.2	0.1
Ischemic stroke	0.3	0.2	0.4	0.2
phosphenes	0.2	0.1	0.1	0.1

Treatment withdrawal includes both permanent and "temporary" without restarting
Source: applicant's SHIFT CSR, Table (12.1.2.3) 4, page 158

In BEAUTIFUL, protocol directed study drug withdrawal for asymptomatic bradycardia totalled 559 patients (10.2%, 7.7%PY) in the ivabradine group versus 46 patients (0.85%, 0.6%PY) in the placebo group. If the study drug was withdrawn for asymptomatic bradycardia or HR < 50 bpm, the investigator did not have to complete an adverse event form. The numbers reported in **Table 61** are based on the adverse event form.

Table 61. Adverse events that led to permanent drug discontinuation - SHIFT and BEAUTIFUL

	SHIFT								BEAUTIFUL							
	Ivabradine N=3260			Placebo N=3278					Ivabradine N=5477			Placebo N=5430				
ADVERSE EVENTS	**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**		**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**	
All	317	(9.7)	5.8	261	(8.0)	4.7	1.22	(1.04, 1.43)	667	(12.2)	9.2	402	(7.4)	4.9	--	--
CHF	42	(1.3)	0.8	46	(1.4)	0.8	0.92	(0.61, 1.39)	50	(0.9)	0.7	34	(0.6)	0.4	1.46	(0.95, 2.25)
Arrhythmia	161	(4.9)	3.0	114	(3.5)	2.1	1.42	(1.12, 1.80)	416	(7.6)	5.7	199	(3.7)	2.4	2.07	(1.76, 2.44)
Supraventricular	105	(3.2)	1.9	83	(2.5)	1.5	1.27	(0.96, 1.69)	133	(2.4)	1.8	118	(2.2)	1.4	1.12	(0.88, 1.43)
AF or AFL	104	(3.2)	1.9	82	(2.5)	1.5	1.28	(0.96, 1.70)	132	(2.4)	1.8	118	(2.2)	1.4	1.11	(0.87, 1.42)
Atrial fibrillation	98	(3.0)	1.8	78	(2.4)	1.4	1.26	(0.94, 1.69)	117	(2.1)	1.6	103	(1.9)	1.3	1.13	(0.87, 1.47)
Ventricular arrhythmia	12	(0.4)	0.2	21	(0.6)	0.4	0.57	(0.28, 1.16)	18	(0.3)	0.2	33	(0.6)	0.4	0.54	(0.30, 0.96)
Ventricular tachycardia	5	(0.2)	0.1	12	(0.4)	0.2	0.42	(0.15, 1.19)	8	(0.1)	0.1	23	(0.4)	0.3	0.34	(0.15, 0.76)
Ventricular fibrillation	2	(0.1)	0.0	3	(0.1)	0.1	0.67	(0.11, 4.01)	3	(0.1)	0.0	6	(0.1)	0.1	0.50	(0.13, 2.00)
Sick sinus syndrome	5	(0.2)	0.1	-	-	-	-	-	5	(0.1)	0.1	-	-	-	-	-
Tachycardia	7	(0.2)	0.1	5	(0.2)	0.1	1.41	(0.45, 4.44)	16	(0.3)	0.2	16	(0.3)	0.2	0.99	(0.50, 1.98)
PVCs (ventricular extra systoles)	5	(0.2)	0.1	4	(0.1)	0.1	1.26	(0.34, 4.69)	5	(0.1)	0.1	4	(0.1)	0.0	1.24	(0.33, 4.62)
Bradycardia, HR decreased	38	(1.2)	0.7	9	(0.3)	0.2	4.25	(2.06, 8.77)	261	(4.8)	3.6	48	(0.9)	0.6	5.39	(3.97, 7.32)
Heart rate decreased	23	(0.7)	0.4	5	(0.2)	0.1	4.63	(1.76, 12.16)	~~114~~	~~(2.1)~~	~~1.6~~	~~14~~	~~(0.3)~~	~~0.2~~	~~8.07~~	~~(4.64, 14.04)~~
Bradycardia	15	(0.5)	0.3	4	(0.1)	0.1	3.77	(1.25, 11.35)	147	(2.7)	2.0	34	(0.6)	0.4	4.29	(2.96, 6.22)
Syncope	1	(0.0)	0.0	2	(0.1)	0.0	0.50	(0.05, 5.51)	4	(0.1)	0.1	6	(0.1)	0.1	0.66	(0.19, 2.34)
Stroke, ICH, TIA	10	(0.3)	0.2	12	(0.4)	0.2	0.84	(0.36, 1.94)	23	(0.4)	0.3	15	(0.3)	0.2	1.52	(0.79, 2.91)
Stroke (ischemic, hemorrhagic)	9	(0.3)	0.2	12	(0.4)	0.2	0.75	(0.32, 1.78)	18	(0.3)	0.2	14	(0.3)	0.2	1.27	(0.63, 2.55)
Ischemic stroke	9	(0.3)	0.2	8	(0.2)	0.1	1.13	(0.44, 2.93)	11	(0.2)	0.2	7	(0.1)	0.1	1.56	(0.61, 4.02)

	SHIFT								BEAUTIFUL							
	Ivabradine N=3260			Placebo N=3278					Ivabradine N=5477			Placebo N=5430				
ADVERSE EVENTS	**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**		**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**	
elevated BUN or Cr, anuria, ARF, CRF, oliguria	2	(0.1)	0.0	2	(0.1)	0.0	1.01	(0.14, 7.17)	11	(0.2)	0.2	9	(0.2)	0.1	1.21	(0.50, 2.92)
Conduction disturbance	11	(0.3)	0.2	5	(0.2)	0.1	2.21	(0.77, 6.35)	17	(0.3)	0.2	19	(0.3)	0.2	0.89	(0.46, 1.71)
AV block	10	(0.3)	0.2	4	(0.1)	0.1	2.51	(0.79, 8.00)	15	(0.3)	0.2	15	(0.3)	0.2	0.99	(0.48, 2.02)
Complete or third degree AV block	9	(0.3)	0.2	3	(0.1)	0.1	3.02	(0.82, 11.15)	9	(0.2)	0.1	9	(0.2)	0.1	0.99	(0.39, 2.49)
Hypertension, BP increased	1	(0.0)	0.0	.		.	.	(., .)	1	(0.0)	0.0	3	(0.1)	0.0	0.33	(0.03, 3.17)
dyspepsia, N, V, indigestion, epigastric pain, gastritis, duodenitis, H pylori infection	9	(0.3)	0.2	7	(0.2)	0.1	1.29	(0.48, 3.46)	10	(0.2)	0.1	15	(0.3)	0.2	0.66	(0.30, 1.47)
phosphenes, visual brightness	7	(0.2)	0.1	4	(0.1)	0.1	1.76	(0.52, 6.01)	22	(0.4)	0.3	5	(0.1)	0.1	4.36	(1.65, 11.51)
Diplopia	1	(0.0)	0.0	.		.	.	(., .)	1	(0.0)	0.0					

Note that this is not an inclusive list of all drug discontinuations for adverse events.
The numbers “HR decreased” for BEAUTIFUL are struck out because the investigator was not obligated to report protocol driven drug discontinuations for asymptomatic bradycardia. Thus, the rate is underestimated.
Reviewer’s analysis: be\LD2dDC_mycatB, bs\data\LD2d\create table all. Applicant’s data: SHIFT, BEAUTIFUL\adven

7.3.4 Significant Adverse Events

The overall incidence of severe adverse events was just slightly higher in subjects treated with placebo compared to ivabradine, 14.9%PY vs. 14.3 %PY. **Table 64** highlights some of the adverse events, focusing on those for which the risk was greater with ivabradine or listing those that have shown up as serious, reasons for discontinuation, or common.

The severe adverse events that had greater risk in those treated with ivabradine compared to placebo in SHIFT included arrhythmias (atrial fibrillation, ventricular fibrillation, and bradycardia), conduction disturbance (mainly AV block). The list of severe adverse events of frequency greater 1 % is similar to the list of SAE (the incidence is just less). One difference relative to the SAEs however, is that for acute MI, the severity was greater in ivabradine treated subjects compared to placebo.

The applicant did an analysis of emergent adverse events that required added therapy or a dose increase of an ongoing treatment. Preferred terms for which the incidence was greater with ivabradine are highlighted in the next table.

Table 62. Adverse events requiring added therapy or dose increase - SHIFT

Preferred term	Ivabradine		Placebo	
	%	%PY	%	%PY
All	55.9	33.3	54.7	32.7
Atrial fibrillation	6.1	3.7	4.9	2.9
BP inadequately controlled	6.1	3.6	5.2	3.1

Not inclusive list. Results shown by randomized treatment.
Source: applicant's SHIFT CSR, page 156

The applicant did an analysis of emergent adverse events that study drug reduction. Preferred terms for which the incidence was greater with ivabradine are highlighted in the next table. Note that the reduction in dose for HR was also protocol driven.

Table 63. Adverse events requiring study drug reduction - SHIFT

Preferred term	Ivabradine		Placebo	
	%	%PY	%	%PY
All	8.7	5.2	1.8	1.0
HR decreased	3.5	2.1	0.6	0.4
Symptomatic bradycardia	2.7	1.6	0.3	0.2

Not inclusive list. Results shown by randomized treatment.
Source: applicant's SHIFT CSR, page 156

Table 64. Severe adverse events on treatment – SHIFT and BEAUTIFUL

	SHIFT								BEAUTIFUL							
	Ivabradine N=3260			Placebo N=3278					Ivabradine N=5477			Placebo N=5430				
AE	**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**		**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**	
All	774	(23.7)	14.3	819	(25.0)	14.9	0.95	(0.87, 1.03)	478	(8.7)	6.6	499	(9.2)	6.1	--	--
CHF	259	(7.9)	4.8	325	(9.9)	5.9	0.80	(0.68, 0.93)	200	(3.7)	2.8	217	(4.0)	2.7	0.91	(0.75, 1.10)
Arrhythmia	85	(2.6)	1.6	60	(1.8)	1.1	1.42	(1.02, 1.97)	96	(1.8)	1.3	80	(1.5)	1.0	1.19	(0.89, 1.60)
Supraventricular	38	(1.2)	0.7	24	(0.7)	0.4	1.59	(0.96, 2.64)	40	(0.7)	0.6	33	(0.6)	0.4	1.20	(0.76, 1.90)
AF or AFL	37	(1.1)	0.7	23	(0.7)	0.4	1.62	(0.96, 2.72)	39	(0.7)	0.5	30	(0.6)	0.4	1.29	(0.80, 2.07)
Atrial fibrillation	30	(0.9)	0.6	17	(0.5)	0.3	1.77	(0.98, 3.20)	25	(0.5)	0.3	24	(0.4)	0.3	1.03	(0.59, 1.80)
Ventricular arrhythmia	40	(1.2)	0.7	35	(1.1)	0.6	1.15	(0.73, 1.81)	35	(0.6)	0.5	46	(0.8)	0.6	0.75	(0.48, 1.16)
Ventricular tachycardia	15	(0.5)	0.3	21	(0.6)	0.4	0.72	(0.37, 1.39)	14	(0.3)	0.2	31	(0.6)	0.4	0.45	(0.24, 0.84)
Ventricular fibrillation	21	(0.6)	0.4	11	(0.3)	0.2	1.92	(0.93, 3.98)	16	(0.3)	0.2	13	(0.2)	0.2	1.22	(0.59, 2.53)
Sick sinus syndrome	3	(0.1)	0.1	-	-	-	-	-	3	(0.1)	0.0	-	-	-	-	-
Tachycardia	8	(0.2)	0.1	7	(0.2)	0.1	1.15	(0.42, 3.17)	15	(0.3)	0.2	10	(0.2)	0.1	1.49	(0.67, 3.31)
PVCs (ventricular extra systoles)	3	(0.1)	0.1	1	(0.0)	0.0	3.02	(0.31, 29.0)	1	(0.0)	0.0	2	(0.0)	0.0	0.50	(0.05, 5.51)
Bradycardia, HR decreased	9	(0.3)	0.2	1	(0.0)	0.0	9.05	(1.15, 71.3)	21	(0.4)	0.3	2	(0.0)	0.0	10.41	(2.44, 44.38)
Heart rate decreased	2	(0.1)	0.0	.		.	.	-	4	(0.1)	0.1	.		.	.	-
Bradycardia	7	(0.2)	0.1	1	(0.0)	0.0	7.04	(0.87, 57.1)	17	(0.3)	0.2	2	(0.0)	0.0	8.43	(1.95, 36.47)
Syncope	3	(0.1)	0.1	9	(0.3)	0.2	0.34	(0.09, 1.25)	6	(0.1)	0.1	11	(0.2)	0.1	0.54	(0.20, 1.46)
CAD, myocardial ischemia	123	(3.8)	2.3	102	(3.1)	1.9	1.21	(0.93, 1.57)	157	(2.9)	2.2	202	(3.7)	2.5	0.77	(0.63, 0.95)
ACS (AMI and unstable angina)	121	(3.7)	2.2	100	(3.1)	1.8	1.22	(0.94, 1.58)	151	(2.8)	2.1	198	(3.6)	2.4	0.76	(0.62, 0.94)
Acute MI	87	(2.7)	1.6	68	(2.1)	1.2	1.29	(0.94, 1.77)	107	(2.0)	1.5	130	(2.4)	1.6	0.82	(0.64, 1.06)

	SHIFT								BEAUTIFUL							
	Ivabradine N=3260			Placebo N=3278					Ivabradine N=5477			Placebo N=5430				
AE	**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**		**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**	
Angina (includes USA, angina pectoris)	38	(1.2)	0.7	47	(1.4)	0.9	0.81	(0.53, 1.24)	44	(0.8)	0.6	78	(1.4)	1.0	0.56	(0.39, 0.81)
Unstable angina	31	(1.0)	0.6	35	(1.1)	0.6	0.89	(0.55, 1.44)	40	(0.7)	0.6	68	(1.3)	0.8	0.58	(0.39, 0.86)
Angina pectoris	7	(0.2)	0.1	13	(0.4)	0.2	0.54	(0.22, 1.35)	4	(0.1)	0.1	10	(0.2)	0.1	0.40	(0.13, 1.27)
Infection, all	57	(1.7)	1.1	87	(2.7)	1.6	0.66	(0.47, 0.92)	71	(1.3)	1.0	73	(1.3)	0.9	0.96	(0.69, 1.33)
Pneumonia	27	(0.8)	0.5	33	(1.0)	0.6	0.82	(0.49, 1.36)	28	(0.5)	0.4	25	(0.5)	0.3	1.11	(0.65, 1.90)
Stroke, ICH, TIA	31	(1.0)	0.6	49	(1.5)	0.9	0.64	(0.41, 1.00)	53	(1.0)	0.7	46	(0.8)	0.6	1.14	(0.77, 1.69)
Stroke (ischemic, hemorrhagic)	30	(0.9)	0.6	45	(1.4)	0.8	0.67	(0.42, 1.06)	48	(0.9)	0.7	41	(0.8)	0.5	1.16	(0.77, 1.76)
Ischemic stroke	22	(0.7)	0.4	32	(1.0)	0.6	0.69	(0.40, 1.18)	28	(0.5)	0.4	22	(0.4)	0.3	1.26	(0.72, 2.20)
GI bleed	13	(0.4)	0.2	7	(0.2)	0.1	1.87	(0.75, 4.68)	9	(0.2)	0.1	12	(0.2)	0.1	0.74	(0.31, 1.75)
elevated BUN or Cr, anuria, ARF, CRF, oliguria	16	(0.5)	0.3	16	(0.5)	0.3	1.01	(0.51, 2.02)	23	(0.4)	0.3	14	(0.3)	0.2	1.63	(0.84, 3.16)
Renal failure acute	8	(0.2)	0.1	6	(0.2)	0.1	1.34	(0.47, 3.86)	12	(0.2)	0.2	5	(0.1)	0.1	2.38	(0.84, 6.75)
Conduction disturbance	17	(0.5)	0.3	5	(0.2)	0.1	3.42	(1.26, 9.26)	10	(0.2)	0.1	14	(0.3)	0.2	0.71	(0.32, 1.60)
AV block	16	(0.5)	0.3	5	(0.2)	0.1	3.22	(1.18, 8.78)	9	(0.2)	0.1	12	(0.2)	0.1	0.74	(0.31, 1.75)
Complete or third degree AV block	11	(0.3)	0.2	4	(0.1)	0.1	2.77	(0.88, 8.69)	7	(0.1)	0.1	10	(0.2)	0.1	0.69	(0.26, 1.81)
Hypertension, BP increased	13	(0.4)	0.2	17	(0.5)	0.3	0.77	(0.37, 1.58)	6	(0.1)	0.1	12	(0.2)	0.1	0.50	(0.19, 1.33)
phosphenes, visual brightness	1	(0.0)	0.0	.		.	.	(., .)	1	(0.0)	0.0	.		.	.	(., .)

Note that this is not an inclusive list of all severe adverse events.
Reviewer's analysis: bs\data\LD2d\create table all. Applicant's data: SHIFT, BEAUTIFUL\adven

Reviewer's comment: The applicant presented an analysis of recovery rates in subjects with treatment emergent adverse events. There were some that could be concerning, but more information about the analysis is needed. If significant information is gained from the additional analysis request, this topic will be covered in *an addendum.*

7.3.5 Submission Specific Primary Safety Concerns

7.3.5.1 Bradycardia

Symptomatic bradycardia and heart rate decrease were consistently higher in ivabradine treated subjects compared to placebo; this was true for common adverse events, SAE, and permanent drug discontinuation (See **Table 65**). While it was a common adverse event, associated with a risk of 4-5 times greater than placebo, it was serious in less than 1%. This was likely due in part to the scheduled visits for monitoring HR and adverse events (**Section 7.2.4**), dose changes based on HR and/or symptoms (**Table 50**), and the likelihood that subjects with symptomatic bradycardia will seek medical care. Note that in BEAUTIFUL, subjects were seen more frequently (M3 and M6 vs. M4 and M8) than in SHIFT. Thus, one might expect that subjects in BEAUTIFUL might have more drug discontinuations for asymptomatic bradycardia; and indeed they did (7.7%PY in BEAUTIFUL vs. 0.4%PY in SHIFT; the RR of AE reported discontinuations was 8 in BEAUTIFUL vs 4.6 in SHIFT).[26] In addition, by protocol SHIFT maintained a 2.5 mg BID dose for HR < 50 bpm or signs, symptoms likely due to bradycardia, whereas in BEAUTIFUL this threshold required treatment discontinuation. Whether these practices prevented other adverse events is difficult to conclude. However, BEAUTIFUL did have less vertigo vestibular dysfunction, asthenia, fatigue, weakness, conduction disturbance, ventricular fibrillation, no Torsades (whereas SHIFT had 2 cases in the ivabradine treated subjects), and sick sinus syndrome compared to SHIFT.

Reviewer comment: Labeling should recommend a more frequent monitoring schedule similar to what was used in BEAUTIFUL.

[26] The actual relative risk is higher, since 8 is based on the AE reported discontinuations for asymptomatic bradycardia, which was 1.6%PY (ivabradine) versus 0.2%PY (placebo).

Table 65. Bradycardia and HR decrease adverse events, nonfatalSAE, and permanent drug d/c – SHIFT and BEAUTIFUL

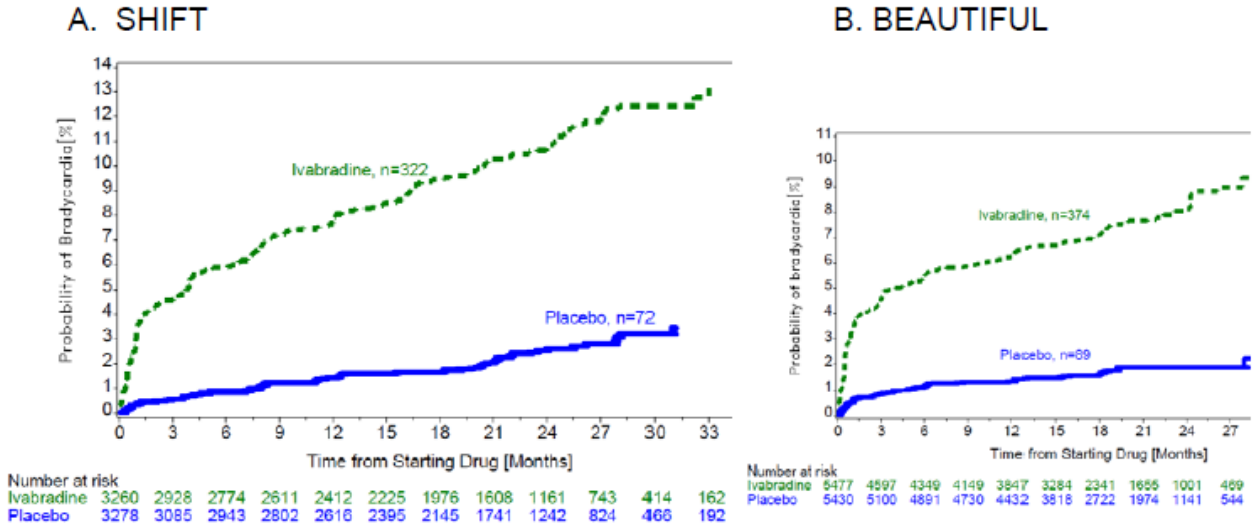
	SHIFT								BEAUTIFUL							
	Ivabradine N=3260			Placebo N=3278					Ivabradine N=5477			Placebo N=5430				
	n	%	%PY	n	%	%PY	RR	(95% CI)	n	%	%PY	n	%	%PY	RR	(95% CI)
Bradycardia, HR decreased																
AE	322	(9.9)	5.9	72	(2.2)	1.3	4.50	(3.50, 5.78)	374	(6.8)	5.2	89	(1.6)	1.1	4.17	(3.32, 5.24)
NF SAE	18	(0.6)	0.3	2	(0.1)	0.0	9.05	(2.10, 38.97)	29	(0.5)	0.4	6	(0.1)	0.1	4.79	(1.99, 11.53)
Drug d/c	38	(1.2)	0.7	9	(0.3)	0.2	4.25	(2.06, 8.77)	22	(0.4)	0.3	3	(0.1)	0.0	7.27	(2.18, 24.28)
Heart rate decreased[1]																
AE	181	(5.6)	3.3	45	(1.4)	0.8	4.04	(2.93, 5.58)	171	(3.1)	2.4	34	(0.6)	0.4	4.99	(3.46, 7.20)
NF SAE	3	(0.1)	0.1						7	(0.1)	0.1					
Drug d/c[2]	23	(0.7)	0.4	5	(0.2)	0.1	4.63	(1.76, 12.16)	114	(2.1)	1.6	14	(0.3)	0.2	8.07	(4.64, 14.04)
Protocol directed w/d[3]									559	(10.2)	7.7	46	(0.9)	0.6	12.05	(8.94, 16.24)
Bradycardia																
AE	148	(4.5)	2.7	28	(0.9)	0.5	5.31	(3.56, 7.93)	206	(3.8)	2.8	56	(1.0)	0.7	3.65	(2.72, 4.89)
NF SAE	15	(0.5)	0.3	2	(0.1)	0.0	7.54	(1.73, 32.95)	22	(0.4)	0.3	6	(0.1)	0.1	3.64	(1.48, 8.97)
Drug d/c	15	(0.5)	0.3	4	(0.1)	0.1	3.77	(1.25, 11.35)	147	(2.7)	2.0	34	(0.6)	0.4	4.29	(2.96, 6.22)

1. Most of the non-serious "HR decreased" had HRs in the 40 -50 bpm
2. AE form reported discontinuation
3. Applicant's analysis. In BEAUTIFUL investigators did not have to complete an adverse event form for protocol driven d/c.

The time to first symptomatic bradycardia occurred faster (steeper slope) in BEAUTIFUL than in SHIFT (see **Figure 58**). This could be because BEAUTIFUL subjects started at lower HRs (inclusion HR ≥ 60 bpm) than SHIFT subjects (inclusion HR ≥ 70 bpm).

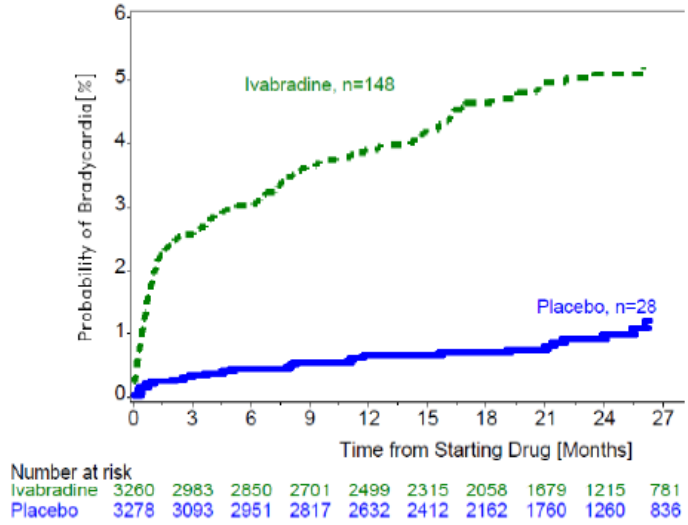
Reviewer comment: In addition, note that the ivabradine curves continue to escalate (steeper than the placebo curve). At first the reviewer thought that the rise could be a reflection of the dose escalations that were allowed in SHIFT. However, dose escalations were not allowed in BEAUTIFUL after the Day 15 visit, yet BEAUTIFUL also exhibits a continued rise in risk of bradycardia. The reviewer will examine this data by subjects who did not change dose and put the results in an addendum. The BEAUTIFUL figure below excludes subjects that did not have an adverse event form completed for a per protocol discontinuation. These data will be requested from the applicant.

Figure 57. Time to first bradycardia (HR decreased & symptomatic) – SHIFT and BEAUTIFUL



Reviewer's analysis: adverse events\tte\create tte brady. \km bradyhr and \km bradyhr_B. Subjects with no event were censored at minimum of last drug intake +2 days or death date. BEAUTIFUL KM curve only includes subjects that had an AE form completed. Investigators did not have to complete an ADVERSE EVENTS form for a per protocol withdrawal.

Figure 58. Time to first symptomatic bradycardia – SHIFT



Reviewer's analysis: adverse events\tte\create tte brady. \km brady. Subjects with no event were censored at minimum of last drug intake +2 days or death date.

The applicant did an analysis of HR and outcomes at Day 28 in SHIFT and BEAUTIFUL. It appears that subjects with lower HRs have less TEAE and less serious TEAE (HR grouped into bins of 5 bpm, starting at < 55 bpm, and going up to ≥ 70 bpm). It does not appear that reducing HR is beneficial for preventing cardiac arrhythmias, however the relationship between achieved HR at Day 28 and cardiac arrhythmias is less clear.[27]

Reviewer comment: This analysis, while reasonable, assumes that the HR achieved at Day 28 is the same HR that subjects will have during the entire trial. This analysis did not include adverse events that occurred prior to Day 28, so subjects who were hospitalized for heart failure or discontinued treatment were not included, and only included adverse events occurring on treatment. Subjects who were not in sinus rhythm at baseline and/or Day 28 were also excluded. The applicant's analysis compared outcomes in subgroups within the ivabradine arm only, based on achieved HR and HRR at Day 28. Analyses to evaluate treatment effect on outcomes within subgroups were not performed since those comparisons are not protected by randomization and are confounded: the subgroup classification is based on post-baseline HR, and the post-baseline HR distributions differ between ivabradine and placebo arms. Since HR inclusion criteria was lower in BEAUTIFUL the applicant performed their HR outcomes analyses in those subjects whose baseline HR was ≥ 70 bpm.

[27] The applicant used Standardized Medical Dictionary for Regulatory Activities MedDRA (SMQ) cardiac arrhythmias query (version 9 for SHIFT, version 7 for BEAUTIFUL)

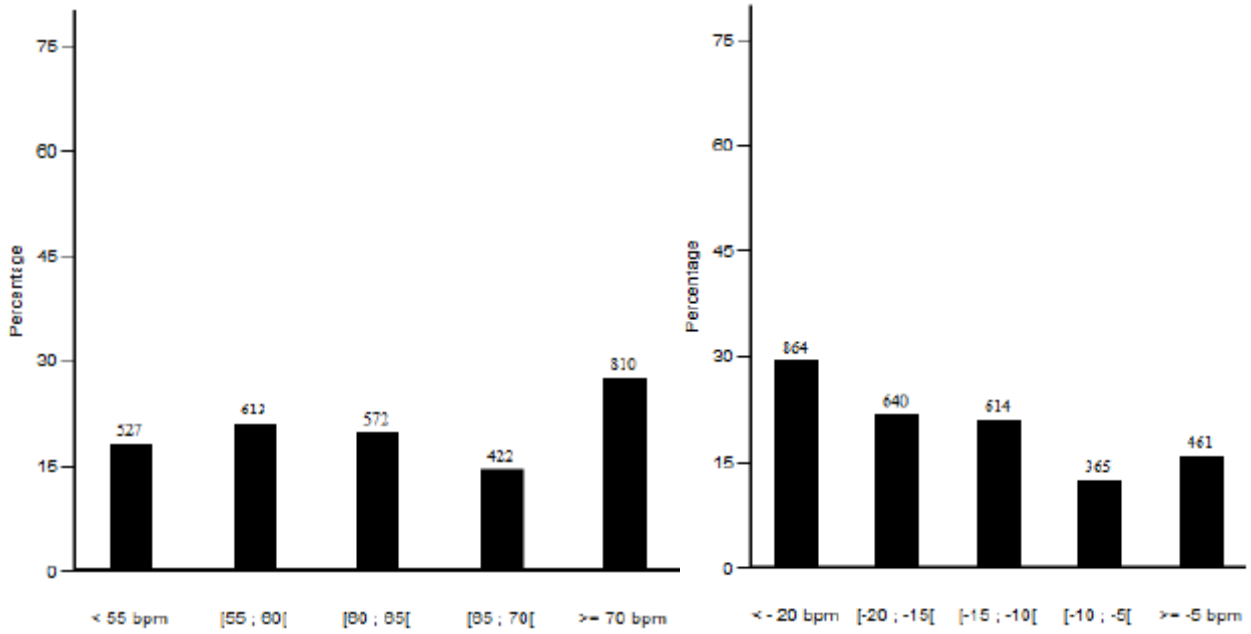
Table 66. Summary of adverse events on or after Day 28 in ivabradine subgroups by achieved HR at Day 28, SHIFT applicant safety set

Achieved Heart Rate at Day 28 (bpm)	N	All Treatment-Emergent Adverse Events n (%)	All Treatment-Emergent Serious Adverse Events n (%)	All Treatment-Emergent Cardiac Arrhythmias Events n (%)	All Treatment-Emergent Serious Cardiac Arrhythmias Events n (%)
ALL	2944	2097 (71.23)	1203 (40.86)	903 (30.67)	393 (13.35)
< 55	527	358 (67.93)	185 (35.10)	175 (33.21)	69 (13.09)
≥ 55; < 60	613	423 (69.00)	221 (36.05)	183 (29.85)	83 (13.54)
≥ 60; < 65	572	415 (72.55)	239 (41.78)	193 (33.74)	83 (14.51)
≥ 65; < 70	422	307 (72.75)	177 (41.94)	132 (31.28)	61 (14.45)
≥ 70	810	594 (73.33)	381 (47.04)	220 (27.16)	97 (11.98)

N: number of subjects in the analysis set; n: number of subjects with at least one emergent adverse event; %: (n/N)*100. bpm: beats per minute
Source: Appendix Table 61 to Appendix Table 64

The achieved HR at day 28 in the ivabradine arm in SHIFT is shown in the next Figure. The data looked similar for subjects in BEAUTIFUL, except that less subjects in BEAUTIFUL achieved a change in HR of more than -20 bpm.

Figure 59. Achieved HR (left) and change in HR (right) at Day 28 - SHIFT



Source: Applicant's HR vs Outcome report. Adapted from Figure 3 & 4. FORM2-UNP01 and UNP02

In SHIFT, as the achieved HR got lower, there were more subjects on beta-blockers at baseline, lower baseline HR, less diabetics, less NYHA Class III/IV, and less current smokers.[28] As achieved HR got lower, more subjects tended to be taking at least 50% of the target beta-blocker dose (although in the HR group 65 ≤ HR < 70, 59% were on 50% beta-blocker and 31% wereo on 100 % beta-blocker target dose compared to 60.4% and 28.2%, respectively in the HR < 55 bpm group). Subjects with greatest HRR, tended to have higher baseline HR and less diabetes.[29] There was not a noticeable difference or trend in baseline beta-blocker use. The group with a change in HR of 5 < HR ≤ 10 had the most subjects taking at least 50% and 100% of the target bet blocker dose (57.5% and 29%, respectively).

In SHIFT, there was not a trend for more cardiac arrhythmia events as HR declined. As expected, the incidence of bradycardia and "HR decreased" increased as achieved HR declined (3.8% of subjects with bradycardia in the HR < 55 bpm group). There was not a trend for serious cardiac arrhythmia events as HR declined.

In SHIFT, there were less serious TEAE as the HRR increased. The trend for serious treatment emergent cardiac arrhythmias as the HRR increased was less clear. The group who achieved a -10 < HR ≤ -15 had 14.7% of subjects with serious treatment emergent cardiac arrhythmias, and the group who achieved a HRR of > 20 bpm had 14.1% of subjects with serious treatment emergent cardiac arrhythmias. There were no noticeable trends in preferred cardiac arrhythmia term (including bradycardia) as the HRR increased, except for the "HR decreased" term.

In sum, the applicants analysis of HR and safety outcomes showed that lower achieved HR were associated with more bradycardia. Other cardiac arrhythmias did not appear to be related to the achived HR or HRR.

7.3.5.2 Atrial Fibrillation

Atrial fibrillation was one of the most common adverse events, SAE, reason for drug discontinuation, and adverse event requiring added therapy where the rates were higher in ivabradine treated subjects compared to placebo treated subjects (see **Table 68**). The reviewer combined atrial fibrillation and atrial flutter for most analyses, but also examined the events separately.

Reviewer's comment: There is a clear separation of atrial fibrillation/flutter between ivabradine and placebo treated subjects (see ***Figure 60, Figure 61, Figure 62****). The onset of separation, however, differs between the three Phase 3 trials; SIGNIFY ~1-2 months, SHIFT ~6 months, and BEAUTIFUL ~ 12 months. It is unclear why this might be*

[28] BEAUTIFUL subjects appeared similar except that there was no trend for current smokers. Information on beta-blocker dose not available.
[29] BEAUTIFUL subjects also higher baseline HR and were less likely to be NYHA Class III. There was no difference in baseline beta-blocker use.

so. All explorations are post hoc, and no definitive conclusions have been made at this time.

There are some likely mechanisms for ivabradine induced atrial fibrillation. 1) In heart failure, HCN channels and I_f are upregulated in atrial myocytes, which may increase automaticity, produce ectopic foci, and contribute to re-entrant pathways through the atria, increasing the incidence of atrial fibrillation and other atrial tachyarrhythmias. 2) There are f-channel expressing pacemaker cells in pulmonary veins.[30,31] Clinical electrophysiology studies in patients has demonstrated that rapid focal activity originating from the pulmonary vein can trigger and maintain atrial fibrillation.[32,33]

The safety reviewer believes that ivabradine causes atrial fibrillation. In the clinical trials, the onset of permanent atrial fibrillation was a condition for drug withdrawal. The safety reviewer believes that ivabradine should not be used in patients with permanent atrial fibrillation or a history of atrial fibrillation.

As part of the evaluation of atrial fibrillation, the reviewer also examined strokes. The two studies appeared to show different results. In SHIFT ivabradine treated subjects did not have a higher incidence of stroke compared to placebo treated subjects. BEAUTIFUL showed the opposite.

Reviewer comment: With ~300 subjects per arm with atrial fibrillation, the sample size is not large enough to make any definitive conclusions about stroke risk from atrial fibrillation in these trials. However, I will examine the data by subjects with / without atrial fibrillation and place that analysis in an addendum.

[30] Chen YC, Pan NH, Cheng CC, Higa S, Chen YJ, & Chen SA (2009). Heterogeneous expression of potassium currents and pacemaker currents potentially regulates arrhythmogenesis of pulmonary vein cardiomyocytes. *J Cardiovasc Electrophysiol* **20**, 1039-1045.
[31] Suenari K, Cheng CC, Chen YC, Lin YK, Nakano Y, Kihara Y, Chen SA, & Chen YJ (2012). Effects of ivabradine on the pulmonary vein electrical activity and modulation of pacemaker currents and calcium homeostasis. *J Cardiovasc Electrophysiol* **23**, 200-206.
[32] Von Bary C, Weber S, Dornia C, et al. Evaluation of pulmonary vein stenosis after pulmonary vein isolation using a novel circular mapping and ablation catheter (PVAC) Circ Arrhythm Electrophysiol. 2011;4:630–636.
[33] Chen YJ, Chen SA, Chang MS, et al. Arrhythmogenic activity of cardiac muscle in pulmonary veins of the dog: implication for the genesis of atrial fibrillation. Cardiovasc Res. 2000;48:265–273.

Table 67. Strokes during the trial – SHIFT & BEAUTIFUL

	SHIFT						BEAUTIFUL					
	Ivabradine N=3260		Placebo N=3278				Ivabradine N=5477		Placebo N=5430			
Type	%	%PY	%	%PY	RR	(95% CI)	%	%PY	%	%PY	RR	(95% CI)
cerebral ischemia (stroke, ICH, TIA)	(3.0)	1.8	(3.6)	2.2	0.82	(0.63, 1.07)	(2.7)	2.1	(2.5)	1.7	1.07	(0.85, 1.34)
Stroke, TIA	(2.9)	1.7	(3.4)	2.0	0.85	(0.65, 1.11)	(2.5)	1.9	(2.5)	1.7	0.99	(0.78, 1.25)
Stroke (ischemic hemorrhagic)	(2.2)	1.3	(2.9)	1.7	0.75	(0.55, 1.01)	(1.9)	1.5	(2.0)	1.3	0.98	(0.75, 1.28)
Ischemic stroke	(1.5)	0.9	(2.3)	1.4	0.64	(0.45, 0.92)	(1.0)	0.8	(1.1)	0.7	0.89	(0.62, 1.28)
systemic embolism	(0.1)	0.1	(0.2)	0.1	0.80	(0.22, 2.98)	(<0.0)[1]	0.0		.	.	(., .)

1. One subject experienced event

Table 68. Atrial fibrillation /flutter adverse events, nonfatal SAE, and drug discontinuation – SHIFT and BEAUTIFUL

	SHIFT								BEAUTIFUL							
	Ivabradine N=3260			Placebo N=3278					Ivabradine N=5477			Placebo N=5430				
	n	%	%PY	n	%	%PY	RR (95% CI)		n	%	%PY	n	%	%PY	RR (95% CI)	
Atrial fibrillation/flutter																
AE	296	(9.1)	5.5	247	(7.5)	4.5	1.20	(1.02, 1.41)	332	(6.1)	4.6	304	(5.6)	3.7	1.08	(0.93, 1.26)
NF SAE	143	(4.4)	2.6	125	(3.8)	2.3	1.15	(0.91, 1.45)	158	(2.9)	2.2	157	(2.9)	1.9	1.00	(0.80, 1.24)
severe	37	(1.1)	0.7	23	(0.7)	0.4	1.62	(0.96, 2.72)	39	(0.7)	0.5	30	(0.6)	0.4	1.29	(0.80, 2.07)
Drug d/c	104	(3.2)	1.9	82	(2.5)	1.5	1.28	(0.96, 1.70)	50	(0.9)	0.7	38	(0.7)	0.5	1.30	(0.85, 1.98)
Atrial fibrillation																
AE	268	(8.2)	4.9	216	(6.6)	3.9	1.25	(1.05, 1.49)	286	(5.2)	4.0	264	(4.9)	3.2	1.07	(0.91, 1.26)
NF SAE	125	(3.8)	2.3	106	(3.2)	1.9	1.19	(0.92, 1.53)	126	(2.3)	1.7	133	(2.4)	1.6	0.94	(0.74, 1.20)
severe	30	(0.9)	0.6	17	(0.5)	0.3	1.77	(0.98, 3.20)	25	(0.5)	0.3	24	(0.4)	0.3	1.03	(0.59, 1.80)
Drug d/c	98	(3.0)	1.8	78	(2.4)	1.4	1.26	(0.94, 1.69)	33	(0.6)	0.5	29	(0.5)	0.4	1.13	(0.69, 1.86)
Drug d/c[1]		(4.2)	2.5		(3.5)	2.1										
Required therapy[2]		(6.1)	3.7		(4.9)	2.9										

1. Applicant's analysis of drug d/c included temporary withdrawals with no restart.
2. Applicant's analysis: requiring added therapy or dose increase

The rate of atrial fibrillation in SIGNIFY was 4.6%, 2.2%PY versus 3.3%, 1.5%PY, ivabradine vs. placebo, respectively. These rates are lower than what was observed in SHIFT and BEAUTIFUL. Being that SIGNIFY was not a study in HF and mean EF% among the trials was lowest in SHIFT, it could be that the up-regulation of atrial myocytes in HF plays a role in the etiology of the atrial fibrillation induced by ivabradine.

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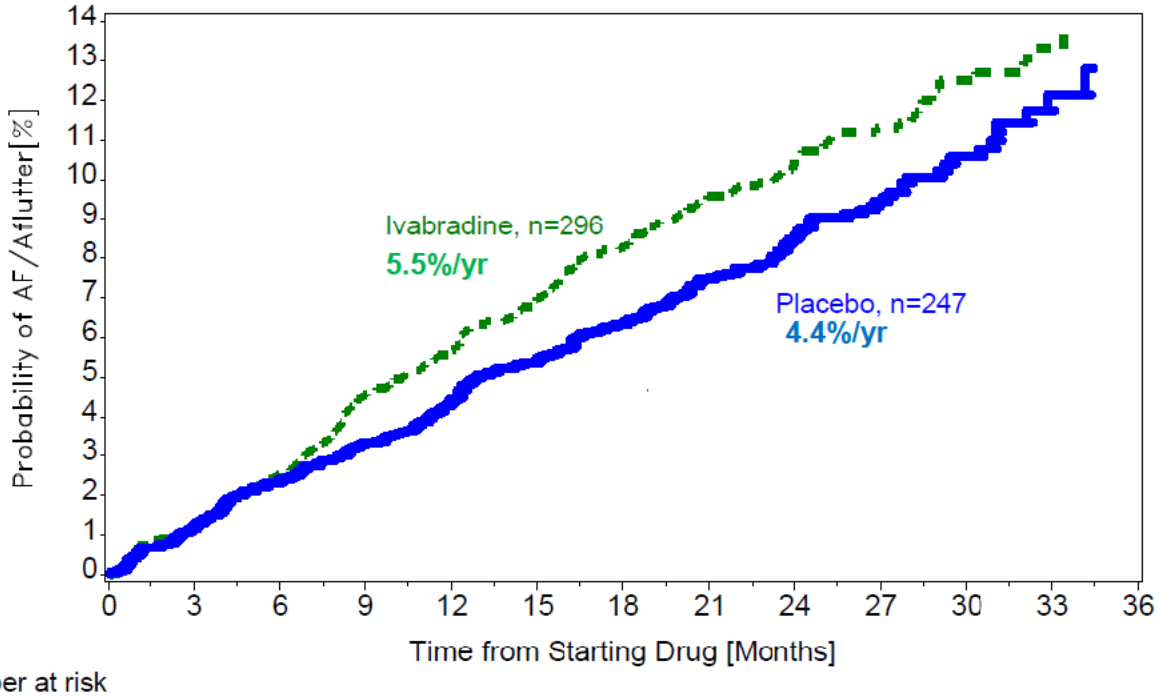
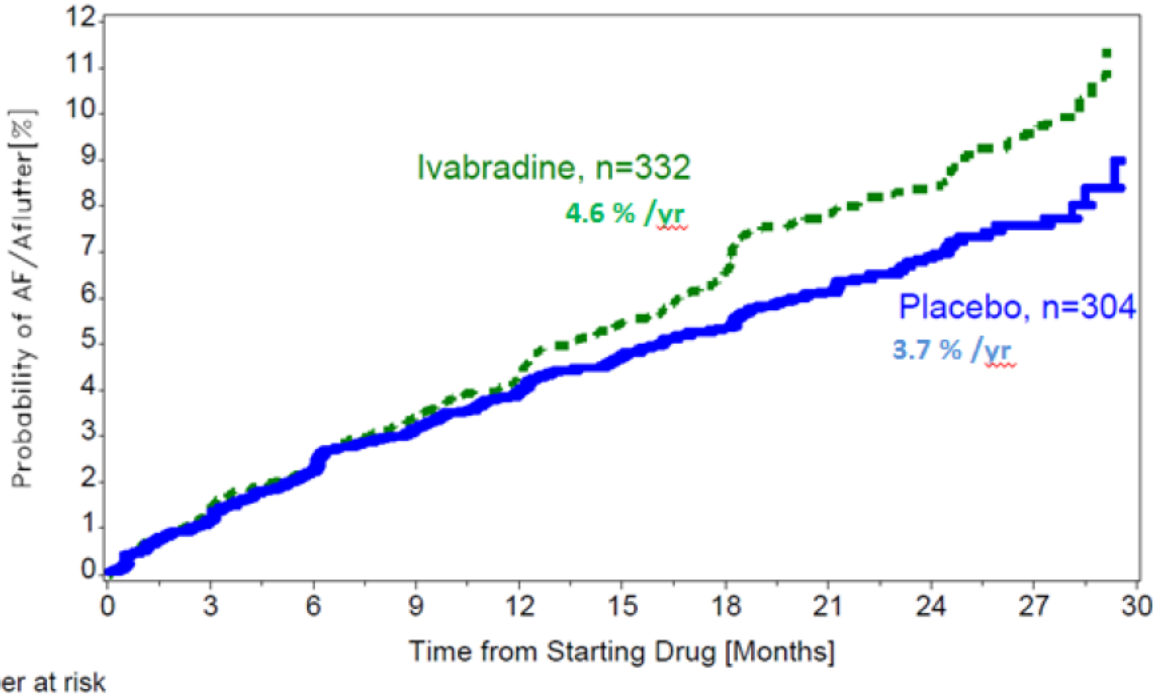
Figure 60. Time to first atrial fibrillation/flutter on treatment - SHIFT



Number at risk												
Ivabradine	3260	3034	2896	2729	2520	2335	2080	1688	1214	778	440	170	36
Placebo	3278	3076	2928	2786	2587	2360	2112	1714	1221	803	463	190	37

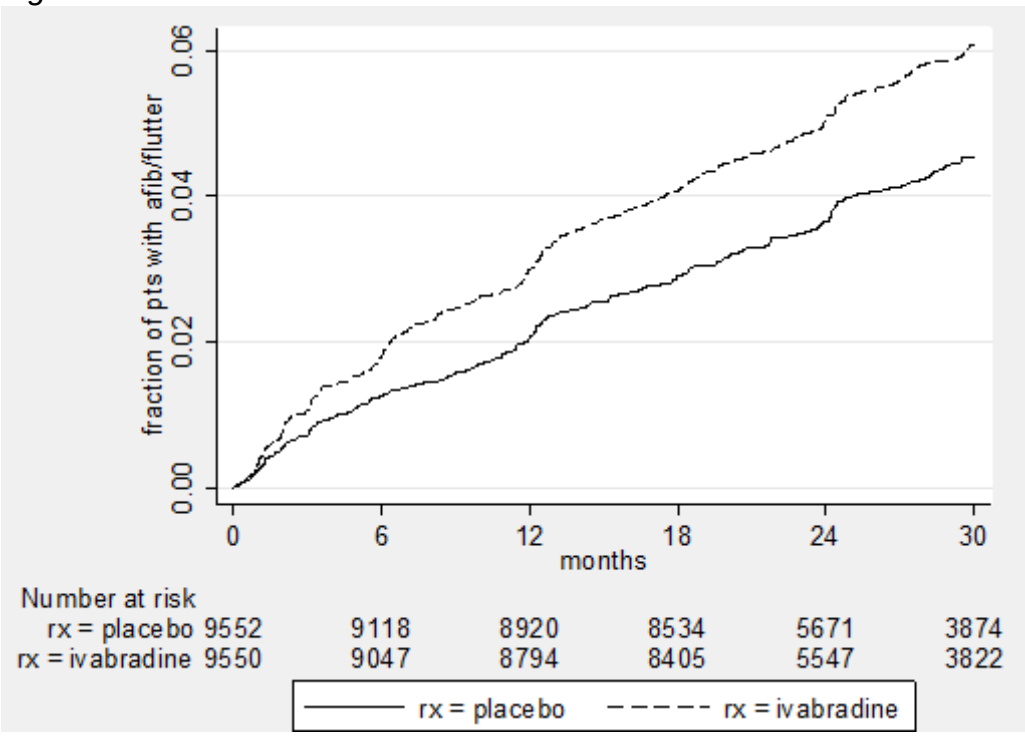
Reviewer's analysis: SHIFT\data\ae\tte\km AF & create tte AF. Applicant's dataset: adven.

Figure 61. Time to first atrial fibrillation/flutter on treatment - BEAUTIFUL



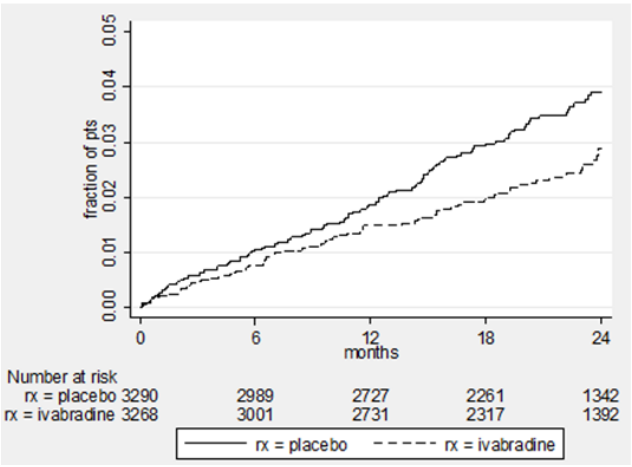
Number at risk											
Ivabradine	5477	4649	4380	4137	3915	3356	2571	1730	1266	547	60
Placebo	5430	5087	4868	4682	4446	3893	2943	2045	1475	656	88

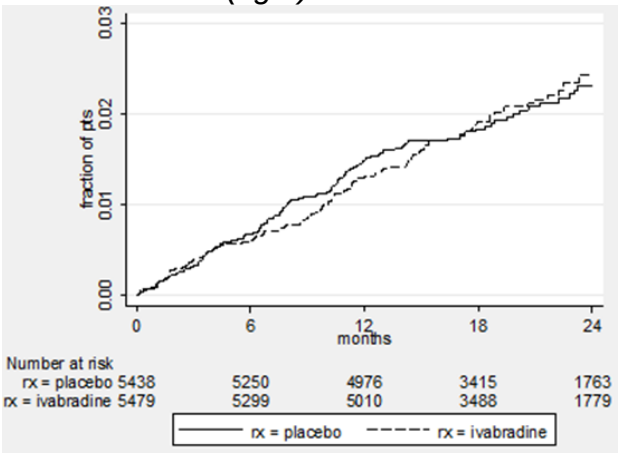
Figure 62. Time to first atrial fibrillation/flutter in SIGNIFY



CDTL's analysis of SIGNIFY

Figure 63. Time to first stroke in SHIFT (left) and BEAUTIFUL (right)





CDTL's analysis

As part of the evaluation of stroke, I also examined blood pressure. Hypertension, increased blood pressure occurred more in ivabradine treated subjects compared to placebo. The relative risk was greater in SHIFT.

Table 69. Hypertension, BP increased – SHIFT & BEAUTIFUL

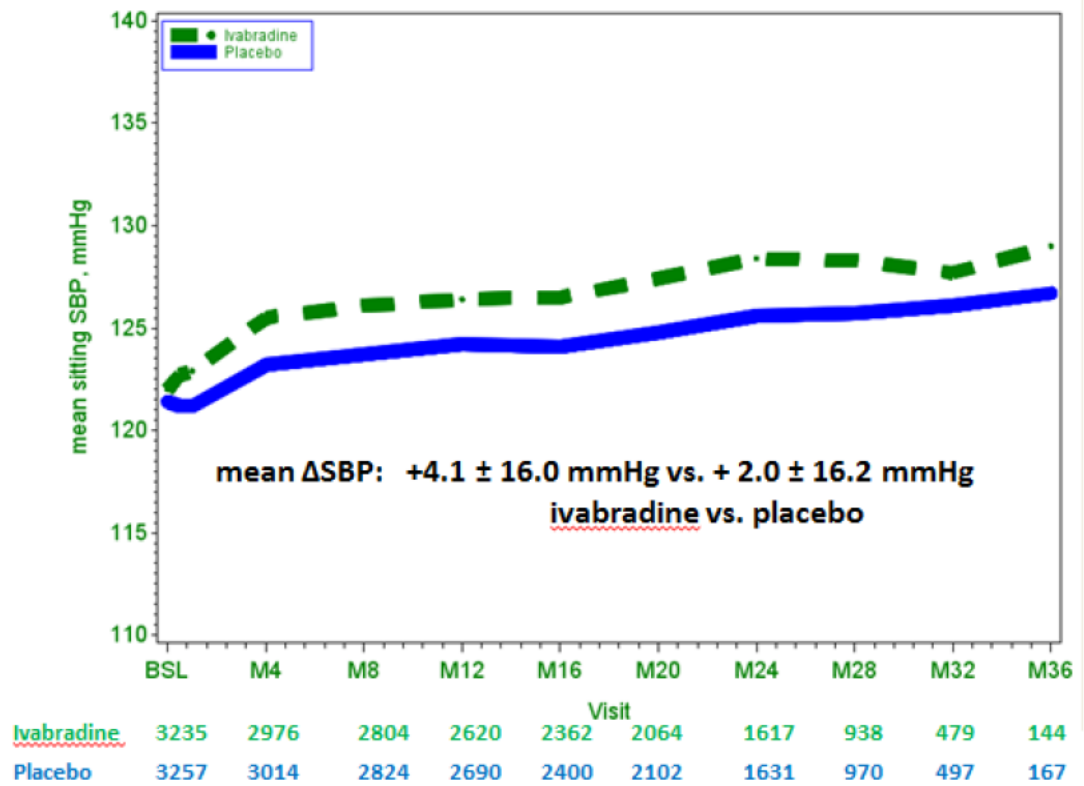
	SHIFT						BEAUTIFUL					
	Ivabradine N=3260		Placebo N=3278				Ivabradine N=5477		Placebo N=5430			
Adverse events	%	%PY	%	%PY	RR	(95% CI)	%	%PY	%	%PY	RR	(95% CI)
On treatment	(8.7)	5.2	(7.7)	4.6	1.13	(0.96, 1.33)	(4.6)	3.5	(4.7)	3.1	0.98	(0.83, 1.16)
During trial	(9.5)	5.7	(8.1)	4.8	1.17	(1.00, 1.37)	(5.1)	3.9	(5.1)	3.4	1.01	(0.86, 1.19)

Reviewer's analysis: BS\data\LD2d\ and study\create table all. Applicant data: adven

Systolic blood pressure increased over time in SHIFT (**Figure 64**), but not in BEAUTIFUL.

Reviewer's comment: It is unclear why the two trials did not show consistent results. However, the reviewer believes that the label should include a description of the BP effects in SHIFT.

Figure 64. Mean sitting SBP over time - SHIFT



Reviewer's analysis:shift\data\BP\p182_nb

7.3.5.3 Acute Renal Failure

The incidence of serious ARF is higher in subjects treated with ivabradine compared to placebo in SHIFT and BEAUTIFUL. There were also more discontinuations for acute renal failure in ivabradine treated subjects.

Table 70. Acute renal failure, anuria on treatment – SHIFT & BEAUTIFUL

	SHIFT						BEAUTIFUL					
	Ivabradine N=3260		Placebo N=3278				Ivabradine N=5477		Placebo N=5430			
Adverse events	%	%PY	%	%PY	RR	(95% CI)	%	%PY	%	%PY	RR	(95% CI)
All	(0.5)	0.3	(0.6)	0.3	0.90	(0.47, 1.73)	(0.4)	0.3	(0.2)	0.1	1.73	(0.85, 3.51)
Serious	(0.4)	0.2	(0.2)	0.1	1.72	(0.68, 4.36)	(0.3)	0.2	(0.1)	0.0	3.47	(1.14, 10.54)
Led to Discontinuation	(<0.0)	0.0	-	-	-	-	(0.1)*	0.1	(0.0)	0.0		
Severe	(0.3)	0.2	(0.2)	0.1	1.51	(0.54, 4.24)	(0.2)	0.2	(0.1)	0.1	2.38	(0.84, 6.75)

Reviewer's analysis:BS\data\LD2d\create table all
*4 subjects

Table 71. Renal failure Preferred term adverse events in SIGNIFY

SIGNIFY Preferred term	Ivabradine N=9538			Placebo N=9543				
ADVERSE EVENTS	n	%	%PY	n	%	%PY	RR (95% CI)	
Renal failure	112	(1.2)	0.6	89	(0.9)	0.4	1.26	(0.96, 1.66)
Acute renal failure	42	(0.4)	0.2	46	(0.5)	0.2	0.91	(0.60, 1.38)
SERIOUS								
Renal failure	38	(0.4)	0.2	27	(0.3)	0.1	1.41	(0.86, 2.31)
Renal failure acute	29	(0.3)	0.1	34	(0.4)	0.2	0.85	(0.52, 1.39)
Anuria	1	(0.0)	0.0	1	(0.0)	0.0	1.00	(0.06, 15.99)
Prerenal failure	1	(0.0)	0.0	1	(0.0)	0.0	1.00	(0.06, 15.99)
Renal failure chronic	33	(0.3)	0.2	17	(0.2)	0.1	1.94	(1.08, 3.48)

Reviewer's analysis: SIGNIFY\data\ae\LD2d

Preliminary analysis of SIGNIFY suggests that renal failure/chronic renal failure is a concern and not ARF. However, subjects in SIGNIFY had a higher mean EF (56%) compared to SHIFT (29%) and BEAUTIFUL (34%). The data suggests that subjects with heart failure may be at risk for renal failure from ivabradine, possibly because their cardiac output is more dependent on heart rate given their reduced stroke volumes.

Reviewer comment: The applicant was asked to examine the renal failure data more closely and attempt to describe the population who might be at greatest risk for developing

ARF from ivabradine. The reviewer will examine these subjects closer to determine if these cases are actually ARF on top of chronic renal failure (as opposed to ARF in subjects with normal renal function).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 72 shows the adverse events that occurred in at least 1% subjects treated with ivabradine and for which the risk of the adverse event was greater with ivabradine compared to placebo (RR >1) in SHIFT.

The Appendix highlights adverse events for which there was a discrepancy between the reviewer and applicant (i.e., acute MI and pneumonia).[34]

The one adverse event that has not been discussed yet are phosphenes. It occurred in 2.8% of subjects treated with ivabradine compared to 0.5% of subjects treated with placebo in SHIFT, a risk that is 5-fold greater with ivabradine. The applicant conducted a special study to evaluate the phosphene adverse events. It is discussed more in **Section 7.4.5 Special Safety Studies/Clinical Trials**.

[34] Hospitalization for MI was an adjudicated efficacy endpoint in BEAUTIFUL. The numbers reported as adverse events differs from the numbers in the hospitalization for MI endpoint.

Table 72. Adverse events occurring in ≥1% of ivabradine treated subjects with RR >1 in SHIFT or BEAUTIFUL

	SHIFT								BEAUTIFUL							
	Ivabradine N=3260			Placebo N=3278					Ivabradine N=5477			Placebo N=5430				
AE	**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**		**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**	
All	2416	(74.1)	44.5	2390	(72.9)	43.4	1.02	(0.99, 1.05)	3048	(55.7)	42.1	3016	(55.5)	37.0	--	--
Arrhythmia	806	(24.7)	14.9	611	(18.6)	11.1	1.33	(1.21, 1.46)	911	(16.6)	12.6	666	(12.3)	8.2	1.36	(1.24, 1.49)
Supraventricular	349	(10.7)	6.4	313	(9.5)	5.7	1.12	(0.97, 1.29)	374	(6.8)	5.2	342	(6.3)	4.2	1.08	(0.94, 1.24)
AF or AFL	296	(9.1)	5.5	247	(7.5)	4.5	1.20	(1.02, 1.41)	332	(6.1)	4.6	304	(5.6)	3.7	1.08	(0.93, 1.26)
Atrial fibrillation	268	(8.2)	4.9	216	(6.6)	3.9	1.25	(1.05, 1.49)	286	(5.2)	4.0	264	(4.9)	3.2	1.07	(0.91, 1.26)
Atrial flutter	37	(1.1)	0.7	35	(1.1)	0.6	1.06	(0.67, 1.68)	55	(1.0)	0.8	48	(0.9)	0.6	1.14	(0.78, 1.68)
Bradycardia, HR decreased	322	(9.9)	5.9	72	(2.2)	1.3	4.50	(3.50, 5.78)	374	(6.8)	5.2	89	(1.6)	1.1	4.17	(3.32, 5.24)
Heart rate decreased	181	(5.6)	3.3	45	(1.4)	0.8	4.04	(2.93, 5.58)	171	(3.1)	2.4	34	(0.6)	0.4	4.99	(3.46, 7.20)
Bradycardia	148	(4.5)	2.7	28	(0.9)	0.5	5.31	(3.56, 7.93)	206	(3.8)	2.8	56	(1.0)	0.7	3.65	(2.72, 4.89)
Ventricular arrhythmia	225	(6.9)	4.1	217	(6.6)	3.9	1.04	(0.87, 1.25)	190	(3.5)	2.6	191	(3.5)	2.3	0.99	(0.81, 1.21)
PVCs (ventricular extra systoles)	144	(4.4)	2.7	138	(4.2)	2.5	1.05	(0.84, 1.32)	116	(2.1)	1.6	108	(2.0)	1.3	1.06	(0.82, 1.37)
Hypertension, BP increased	284	(8.7)	5.2	252	(7.7)	4.6	1.13	(0.96, 1.33)	250	(4.6)	3.5	254	(4.7)	3.1	0.98	(0.83, 1.16)
CAD, myocardial ischemia	246	(7.5)	4.5	234	(7.1)	4.2	1.06	(0.89, 1.26)	330	(6.0)	4.6	401	(7.4)	4.9	0.82	(0.71, 0.94)

	SHIFT								BEAUTIFUL							
	Ivabradine N=3260			Placebo N=3278					Ivabradine N=5477			Placebo N=5430				
AE	**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**		**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**	
ACS (AMI and unstable angina)	229	(7.0)	4.2	220	(6.7)	4.0	1.05	(0.88, 1.26)	306	(5.6)	4.2	371	(6.8)	4.6	0.82	(0.71, 0.95)
Acute MI	116	(3.6)	2.1	103	(3.1)	1.9	1.13	(0.87, 1.47)	147	(2.7)	2.0	166	(3.1)	2.0	0.88	(0.71, 1.10)
Cardiac arrest, SCD, sudden death	186	(5.7)	3.4	188	(5.7)	3.4	0.99	(0.81, 1.21)	206	(3.8)	2.8	187	(3.4)	2.3	1.09	(0.90, 1.32)
Elevated BUN or Cr, anuria, ARF, CRF, oliguria	179	(5.5)	3.3	212	(6.5)	3.8	0.85	(0.70, 1.03)	202	(3.7)	2.8	180	(3.3)	2.2	1.11	(0.91, 1.35)
Blood creatinine increased	56	(1.7)	1.0	46	(1.4)	0.8	1.22	(0.83, 1.80)	58	(1.1)	0.8	54	(1.0)	0.7	1.06	(0.73, 1.53)
Pneumonia	138	(4.2)	2.5	154	(4.7)	2.8	0.90	(0.72, 1.13)	147	(2.7)	2.0	133	(2.4)	1.6	1.10	(0.87, 1.39)
Conduction disturbance	108	(3.3)	2.0	93	(2.8)	1.7	1.17	(0.89, 1.54)	88	(1.6)	1.2	102	(1.9)	1.3	0.86	(0.65, 1.14)
AV block	61	(1.9)	1.1	52	(1.6)	0.9	1.18	(0.82, 1.70)	55	(1.0)	0.8	50	(0.9)	0.6	1.09	(0.74, 1.60)
QRS prolonged, BBB	39	(1.2)	0.7	36	(1.1)	0.7	1.09	(0.69, 1.71)	32	(0.6)	0.4	53	(1.0)	0.7	0.60	(0.39, 0.93)
Solid neoplasia, ALL (benign, malignant, unknown)	96	(2.9)	1.8	83	(2.5)	1.5	1.16	(0.87, 1.55)	134	(2.4)	1.9	148	(2.7)	1.8	0.90	(0.71, 1.13)
Cancer (non-squamous cell)	52	(1.6)	1.0	48	(1.5)	0.9	1.09	(0.74, 1.61)	81	(1.5)	1.1	97	(1.8)	1.2	0.83	(0.62, 1.11)
Phosphenes, visual brightness	91	(2.8)	1.7	18	(0.5)	0.3	5.08	(3.07, 8.40)	206	(3.8)	2.8	46	(0.8)	0.6	4.44	(3.23, 6.10)
Cerebral ischemia (stroke, ICH, TIA)	85	(2.6)	1.6	100	(3.1)	1.8	0.85	(0.64, 1.13)	124	(2.3)	1.7	122	(2.2)	1.5	1.01	(0.79, 1.29)

	SHIFT								BEAUTIFUL							
	Ivabradine N=3260			Placebo N=3278					Ivabradine N=5477			Placebo N=5430				
AE	**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**		**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**	
Bleeding	75	(2.3)	1.4	68	(2.1)	1.2	1.11	(0.80, 1.54)	70	(1.3)	1.0	71	(1.3)	0.9	0.98	(0.71, 1.36)
GI bleed	31	(1.0)	0.6	27	(0.8)	0.5	1.15	(0.69, 1.92)	27	(0.5)	0.4	32	(0.6)	0.4	0.84	(0.50, 1.40)
Transaminases abnormal	76	(2.3)	1.4	72	(2.2)	1.3	1.06	(0.77, 1.46)	66	(1.2)	0.9	87	(1.6)	1.1	0.75	(0.55, 1.03)
Increased transaminases	46	(1.4)	0.8	42	(1.3)	0.8	1.10	(0.73, 1.67)	33	(0.6)	0.5	43	(0.8)	0.5	0.76	(0.48, 1.19)
Diarrhea, colitis, enteritis, proctitis, gastroenteritis, C-diff	64	(2.0)	1.2	69	(2.1)	1.3	0.93	(0.66, 1.30)	109	(2.0)	1.5	97	(1.8)	1.2	1.11	(0.85, 1.46)
Diarrhoea	33	(1.0)	0.6	35	(1.1)	0.6	0.95	(0.59, 1.52)	58	(1.1)	0.8	50	(0.9)	0.6	1.15	(0.79, 1.68)
Asthenia, fatigue, malaise, weakness, narcolepsy	60	(1.8)	1.1	38	(1.2)	0.7	1.59	(1.06, 2.38)	86	(1.6)	1.2	92	(1.7)	1.1	0.93	(0.69, 1.24)
Fatigue	31	(1.0)	0.6	21	(0.6)	0.4	1.48	(0.85, 2.57)	59	(1.1)	0.8	56	(1.0)	0.7	1.04	(0.72, 1.50)
Dizziness	55	(1.7)	1.0	47	(1.4)	0.9	1.18	(0.80, 1.74)	104	(1.9)	1.4	88	(1.6)	1.1	1.17	(0.88, 1.55)
Cholecystitis, cholelithiasis, bile duct stone	47	(1.4)	0.9	59	(1.8)	1.1	0.80	(0.55, 1.17)	59	(1.1)	0.8	58	(1.1)	0.7	1.01	(0.70, 1.45)
Headache	45	(1.4)	0.8	60	(1.8)	1.1	0.75	(0.51, 1.10)	57	(1.0)	0.8	56	(1.0)	0.7	1.01	(0.70, 1.46)
Respiratory tract infection	44	(1.3)	0.8	32	(1.0)	0.6	1.38	(0.88, 2.17)	44	(0.8)	0.6	52	(1.0)	0.6	0.84	(0.56, 1.25)
Bronchitis	41	(1.3)	0.8	39	(1.2)	0.7	1.06	(0.69, 1.64)	77	(1.4)	1.1	90	(1.7)	1.1	0.85	(0.63, 1.15)

	SHIFT								BEAUTIFUL							
	Ivabradine N=3260			Placebo N=3278					Ivabradine N=5477			Placebo N=5430				
AE	**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**		**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**	
Vertigo vestibular dysfunction	36	(1.1)	0.7	17	(0.5)	0.3	2.13	(1.20, 3.78)	53	(1.0)	0.7	53	(1.0)	0.7	0.99	(0.68, 1.45)
Dyspnea, SOB	36	(1.1)	0.7	39	(1.2)	0.7	0.93	(0.59, 1.46)	79	(1.4)	1.1	72	(1.3)	0.9	1.09	(0.79, 1.50)
Gastric or duodenal ulcer, erosion, perforation	32	(1.0)	0.6	23	(0.7)	0.4	1.40	(0.82, 2.39)	31	(0.6)	0.4	35	(0.6)	0.4	0.88	(0.54, 1.42)
Low K	34	(1.0)	0.6	32	(1.0)	0.6	1.07	(0.66, 1.73)	29	(0.5)	0.4	39	(0.7)	0.5	0.74	(0.46, 1.19)
Hypokalaemia	33	(1.0)	0.6	26	(0.8)	0.5	1.28	(0.77, 2.14)	23	(0.4)	0.3	32	(0.6)	0.4	0.71	(0.42, 1.21)
Diabetes mellitus	34	(1.0)	0.6	37	(1.1)	0.7	0.92	(0.58, 1.46)	70	(1.3)	1.0	55	(1.0)	0.7	1.26	(0.89, 1.79)
Diabetes mellitus non-insulin-dependent	31	(1.0)	0.6	29	(0.9)	0.5	1.07	(0.65, 1.77)	12	(0.2)	0.2	15	(0.3)	0.2	0.79	(0.37, 1.69)
Visual disturbance, corneal deposits	27	(0.8)	0.5	10	(0.3)	0.2	2.71	(1.31, 5.59)	60	(1.1)	0.8	38	(0.7)	0.5	1.57	(1.05, 2.35)
Vision blurred	17	(0.5)	0.3	7	(0.2)	0.1	2.44	(1.01, 5.88)	54	(1.0)	0.7	31	(0.6)	0.4	1.73	(1.11, 2.69)

Reviewer's analysis: bs\data\LD2d\create table cuts. Applicant's data: SHIFT, BEAUTIFUL\adven

The next table shows adverse events for which the lower confidence interval of risk was greater than 1, (i.e., the adverse events was significantly worse in subjects treated with ivabradine). These should be described in labelling. It is noted that squamous cell carcinoma was higher in ivabradine treated subjects compared to placebo. The risk was not as high in BEAUTIFUL. These were not cancer trials and screening for cancer was not meticulously done. The reviewer finds it unlikely that ivabradine causes skin cancer.

Table 73. Adverse events with lower confidence interval > 1 in SHIFT

	SHIFT								BEAUTIFUL							
	Ivabradine N=3260			Placebo N=3278					Ivabradine N=5477			Placebo N=5430				
AE	**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**		**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**	
Arrhythmia	806	(24.7)	14.9	611	(18.6)	11.1	1.33	(1.21, 1.46)	911	(16.6)	12.6	666	(12.3)	8.2	1.36	(1.24, 1.49)
AF or AFL	296	(9.1)	5.5	247	(7.5)	4.5	1.20	(1.02, 1.41)	332	(6.1)	4.6	304	(5.6)	3.7	1.08	(0.93, 1.26)
Atrial fibrillation	268	(8.2)	4.9	216	(6.6)	3.9	1.25	(1.05, 1.49)	286	(5.2)	4.0	264	(4.9)	3.2	1.07	(0.91, 1.26)
Bradycardia, HR decreased	322	(9.9)	5.9	72	(2.2)	1.3	4.50	(3.50, 5.78)	374	(6.8)	5.2	89	(1.6)	1.1	4.17	(3.32, 5.24)
Heart rate decreased*	181	(5.6)	3.3	45	(1.4)	0.8	4.04	(2.93, 5.58)	171	(3.1)	2.4	34	(0.6)	0.4	4.99	(3.46, 7.20)
Bradycardia*	148	(4.5)	2.7	28	(0.9)	0.5	5.31	(3.56, 7.93)	206	(3.8)	2.8	56	(1.0)	0.7	3.65	(2.72, 4.89)
Ventricular fibrillation	24	(0.7)	0.4	12	(0.4)	0.2	2.01	(1.01, 4.01)	16	(0.3)	0.2	13	(0.2)	0.2	1.22	(0.59, 2.53)
Phosphenes, visual brightness	91	(2.8)	1.7	18	(0.5)	0.3	5.08	(3.07, 8.40)	206	(3.8)	2.8	46	(0.8)	0.6	4.44	(3.23, 6.10)
Asthenia, fatigue, malaise, weakness, narcolepsy	60	(1.8)	1.1	38	(1.2)	0.7	1.59	(1.06, 2.38)	86	(1.6)	1.2	92	(1.7)	1.1	0.93	(0.69, 1.24)
vertigo vestibular dysfunction	36	(1.1)	0.7	17	(0.5)	0.3	2.13	(1.20, 3.78)	53	(1.0)	0.7	53	(1.0)	0.7	0.99	(0.68, 1.45)
high or third degree AV Block	18	(0.6)	0.3	6	(0.2)	0.1	3.02	(1.20, 7.60)	14	(0.3)	0.2	16	(0.3)	0.2	0.87	(0.43, 1.78)
squamous cell Ca skin	8	(0.2)	0.1	1	(0.0)	0.0	8.04	(1.01, 64.25)	16	(0.3)	0.2	12	(0.2)	0.1	1.32	(0.63, 2.79)

Reviewer's analysis: bs\data\LD2d\create table cuts. Applicant's data: SHIFT, BEAUTIFUL\adv

7.4.2 Laboratory Findings

According to the applicant there were no clinically important mean changes in laboratory parameters in SHIFT. The reviewer plotted the serum creatinine, creatinine clearance, and potassium data and did not observe any noticeable changes from baseline in those labs either. Emergent abnormal values were detected with similar frequency in both treatment groups (**Table 74**). While these are what the data show, it is noted that the adverse event term "blood creatinine increased" was higher in ivabradine treated subjects than placebo treated subjects in SHIFT.

Table 74. Percent emergent abnormal laboratory values – SHIFT

	Ivabradine	Placebo
High		
Serum creatinine	17.4	16.4
ALT	14.7	15.1
AST	12.9	13.1
potassium	13.0	14.0
Low		
hemoglobin	14.3	15.5

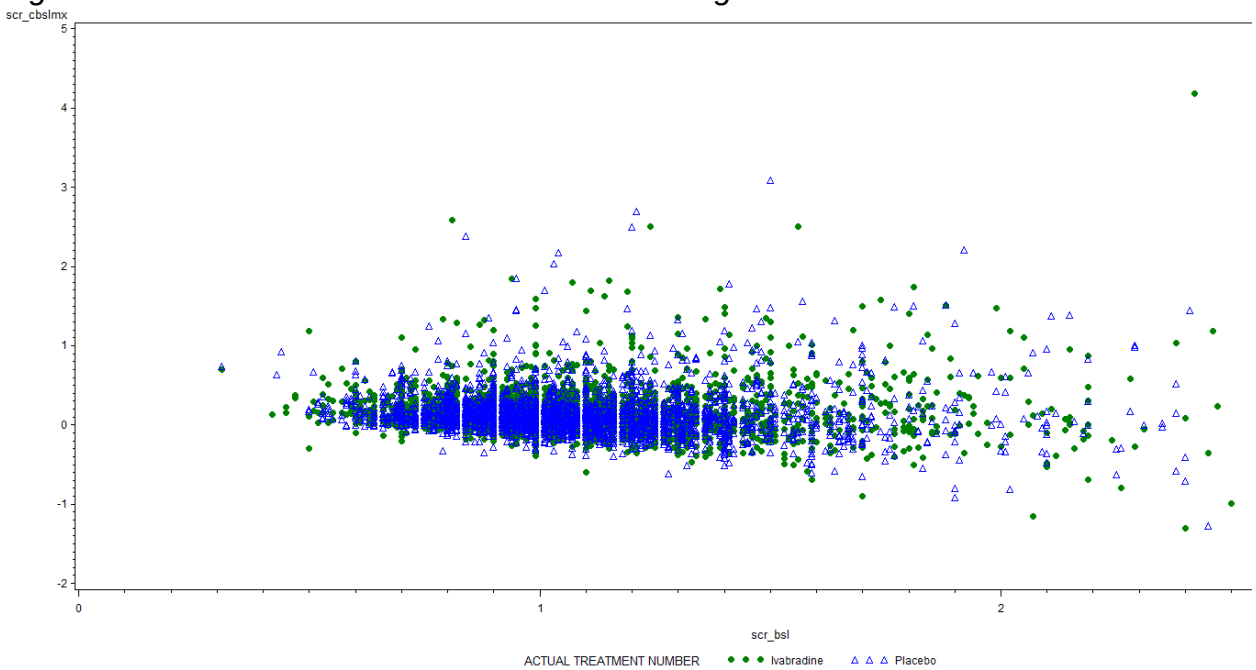
Applicant's analysis. SCS, page 172.

Reviewer comment: In SHIFT, RBC count, WBC count, platelet, and glucose values could not be found in the datasets or CRF despite being collected per protocol, but the adverse event data were checked for significant adverse events related to changes in these values. Eight subjects treated with ivabradine experienced a hematologic adverse event compared to 23 subjects treated with placebo. Thus, there are no concerns about ivabradine induced hematologic adverse events

Serum creatinine

Creatinine's secretion is by an organic cation transporter (OCT). Ivabradine (b) (4) however a drug interaction study with metformin, a substrate for the OCT2 transporter, in healthy subjects showed no difference in peak or total systemic exposure of metformin. Despite the negative finding in humans, the adverse event data in SHIFT and BEAUTIFUL suggests ivabradine might contribute to renal failure, so serum creatinine and CrCL were examined closely. Neither serum creatinine (**Figure 65**) nor CrCL (**Figure 69**) data indicate that there's a clear signal of harm; there were outliers in both treatment groups.

Figure 65. Baseline serum creatinine versus change from baseline - SHIFT



Reviewer's analysis

7.4.3 Vital Signs

Blood pressure and heart rate have already been discussed.

7.4.4 Electrocardiograms (ECGs)

Atrial fibrillation and other cardiac arrhythmias have already been discussed.

7.4.5 Special Safety Studies/Clinical Trials

7.4.5.1 Visual effects

The cardiac current I_f is carried by hyperpolarization-activated, cyclic nucleotide-gated channels (HCN), a family of 4 homologous transmembrane proteins that are expressed in sinoatrial node, brain, and retina (see also **Table 56**). Thus, it is not surprising that ivabradine affects the eye.

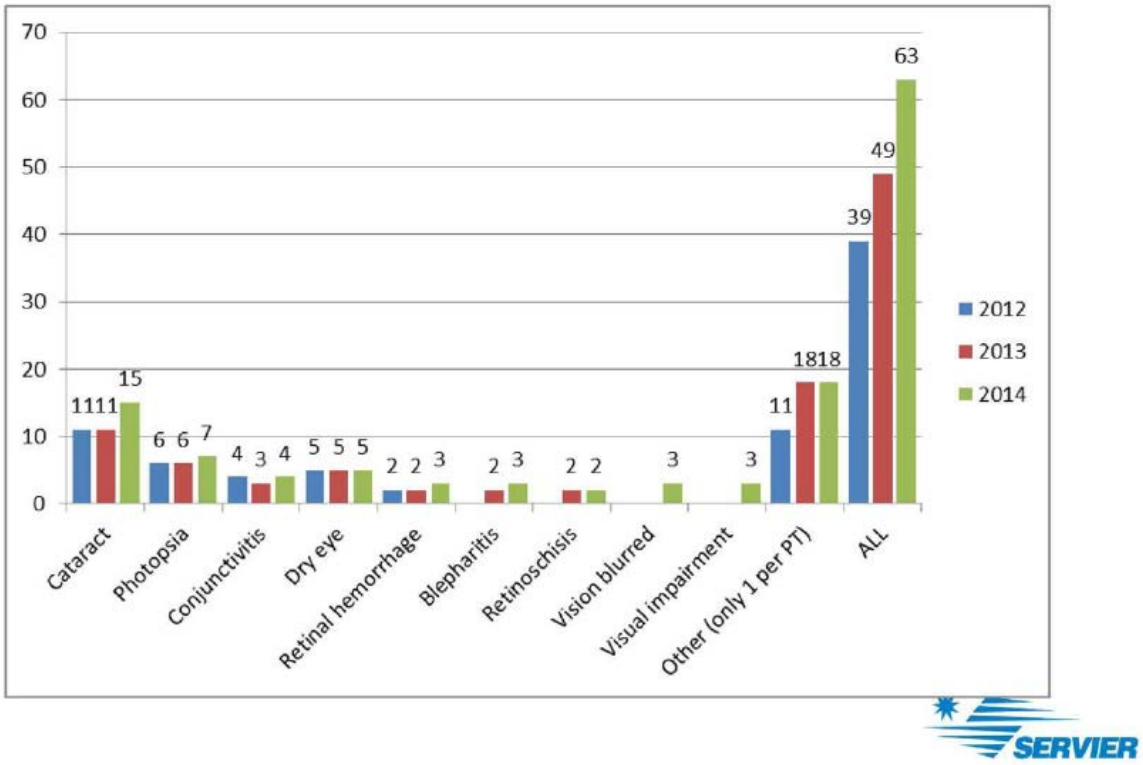
Ivabradine induced visual symptoms start within the first 2 months of treatment. The most predominant effect is phosphenes; uncommon effects include diplopia and visual impairment. Phosphenes may be described as a halo, image decomposition (stroboscopic or kaleidoscopic effects), colored bright lights, or multiple images (retinal persistency).

A one year double blind trial concluded that ivabradine does not cause retinal degeneration. The CHMP asked Servier to conduct Study CL3-16257-067, a 3 year placebo-controlled study in 100 stable angina patients to document the absence of long-term retinal toxicity. Subjects were randomized to placebo or ivabradine 5 mg BID (or 2.5 mg BID in subjects > 75 years or subjects

taking concomitant moderate CYP3A4 inhibitors) titrated up to 7.5 mg BID at Month 1. The dose was to be adjusted based on HR and symptoms. Ivabradine was to be discontinued for HR < 50 bpm or persistent symptoms of bradycardia.

A Scientific Safety Ophthalmic Committee (SSOC) convened in March 2014 to discuss the data from the trial that had enrolled 97 patients, 73 of whom had completed the M36 visit (last visit on treatment), and 68 had completed the M38 visit. The last subject is expected to complete the M38 visit in December 2014. The next meeting was October 2014, and data unblinding is expected in 2015. The committee concluded that the data raised no concerns about long-term exposure to ivabradine. The next figure shows the number of ophthalmic adverse events.

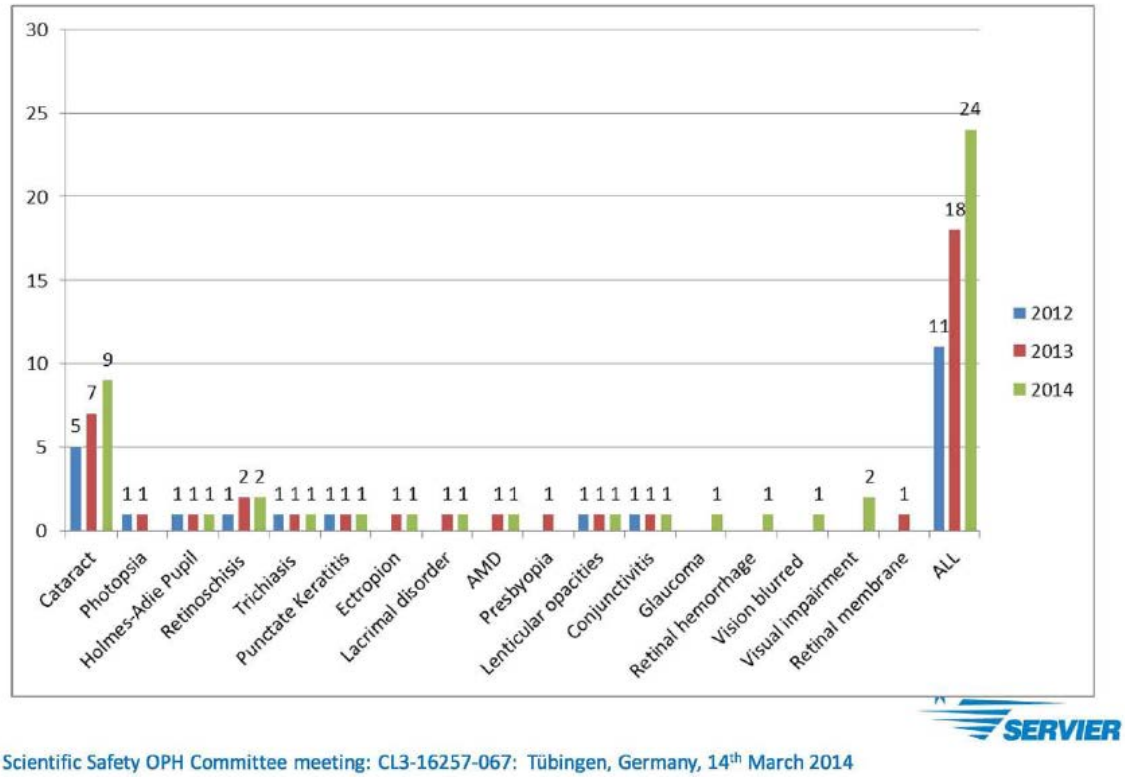
Figure 66. Number of ophthalmic adverse events in Study CL3-16257-067



V.th Scientific Safety OPH Committee meeting: CL3-16257-067: Tübingen, Germany, 14th March 2014

Most subjects recovered from their adverse event. Seven subjects had phosphenes; none were serious or led to treatment interruption; and all recovered. The next figure shows the PT for subjects that did not recover.

Figure 67. Preferred terms for subjects that did not recover in Study CL3-16257-067



7.4.5.2 QT prolongation

A Thorough QT study was not required because the Division thought that it would not adequately assess ivabradine's proarrhythmic liability due to confounding effects on the large decrease in heart rate. Ivabradine and its major metabolite, S18982, were evaluated in vitro and in vivo in dedicated cardiovascular safety pharmacology studies. The nonclinical data showed hERG inhibition and APD prolongation at high concentrations, relative to clinical exposure. There was no evidence of QTc prolongation in vivo in telemetered animals given doses that produce high plasma concentrations relative to clinical exposure. Thus, the nonclinical data suggests a low risk for QT prolongation. However, a drug that lowers heart rate independent of adrenergic or calcium channel blockade can increase the risk of bradycardia dependent arrhythmias, including torsade de pointes.

Two emergent cases of torsade de pointes were observed in ivabradine treated subjects in SHIFT; none in BEAUTIFUL. Both cases were confounded by multiple clinical risk factors that predispose patients to torsade de pointes. One case (Subject 000260) occurred after 2 months on treatment in the setting of severe hypokalemia in a patient taking loop diuretics, with a serum potassium of 2.8 mEq/L upon presentation with ventricular tachycardia.

The other case (Subject 005041) occurred in a patient taking loop diuretics with a history of myocardial infarctions and ischemic cardiomyopathy. Subject 005041's initial arrhythmia was atrial flutter with 1:1 conduction, followed by sustained monomorphic ventricular tachycardia that was treated with the anti-arrhythmic drug lidocaine, and then degenerated into torsade de pointes. Heart failure, structural heart disease, history of myocardial infarction, hypokalemia and treatment with diuretics are known risk factors for torsade de pointes.

Since the introduction of ivabradine on the market, a total of 24 cases of ECG-prolonged QT interval were reported (including one case of long QT syndrome). Considering the overall estimated exposure to ivabradine since marketing authorization (i.e., 1,351,798 patient-years), the overall frequency of reported cases of ECG QT prolongation is 1.77/100,000 PY. In 14 cases, concomitant heart rate lowering drugs were given with ivabradine. In 18 cases, ECG-prolonged QT interval was associated with cardiac events or other ECG abnormalities, especially bradycardia/heart rate decreased (8 cases) and severe ventricular arrhythmias (6 cases). One case of ECG-prolonged QT interval, complicated by ventricular tachycardia, and torsade de pointes in a context of hypokalemia, was reported in a 62 year-old female patient concomitantly treated with furosemide and diltiazem.

Syncope or pre-syncope was reported in 54 patients during the period (3.99/100,000 PY). In 22 cases, bradycardia or heart rate decrease was associated with the event; in 5 cases, complete AV block was concomitant; and in 5 cases, ventricular arrhythmia was concomitant (associated to bradycardia or heart rate decreased in 2 cases). In 47 cases, the patient recovered or was recovering, and in one case, the patient had not recovered at the time of the report. None of these events were fatal. In 6 cases, the outcome is unknown.

Torsade de pointes that occurred post-marketing in patients on ivabradine occurred mostly in the context of known alternate risk factors that predispose to such events (Drew et al, 2010): concomitant loop diuretics (in 8/12 cases), patients with hypokalemia (2 cases documented) in patients receiving other drugs with heart rate lowering activities (7/12 cases) or in patients receiving concomitant contra-indicated or not recommended drug (5/12 cases), like verapamil, diltiazem, fluconazole or macrolide antibiotics). In two cases, QTc prolongation and in one case complete AV block were documented. For the other cases of severe ventricular arrhythmias, a cardiac disease known to be associated with ventricular arrhythmia (CAD, heart failure, valvulopathy) was present in all the cases.

7.4.6 Immunogenicity

This does not appear to have been done. An IR was sent to the applicant.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The dose was titrated to HR and/or symptomatic bradycardia. Phosphenes was a dose limited side effect during the dose finding studies.

7.5.2 Time Dependency for Adverse Events

Time to event analyses were conducted for common adverse events. See specific sections.

7.5.3 Drug-Demographic Interactions

There was a higher incidence of adverse events in subjects aged greater than 65 years old. In the European label, the recommended starting dose is 2.5 mg BID in subjects aged 75 years and older. This is a reasonable recommendation.

Table 75. Applicant's analysis of adverse events by age < 65 years old - SHIFT

	Ivabradine			Placebo			Total		
	N	n (%)	%PY	N	n (%)	%PY	N	n (%)	%PY
Subjects with a TEAE									
Subjects < 65 years of age	1972	1425 (72.3)	41.8	2051	1458 (71.1)	41.9	4023	2883 (71.7)	41.8
Subjects ≥ 65 years of age	1260	989 (78.5)	49.6	1209	934 (77.3)	46.4	2469	1923 (77.9)	48.0
Deaths									
Subjects < 65 years of age	1972	263 (13.3)	7.1	2051	308 (15.0)	8.3	4023	571 (14.2)	7.7
Subjects ≥ 65 years of age	1260	247 (19.6)	10.9	1209	256 (21.2)	11.7	2469	503 (20.4)	11.3
Subjects with a treatment-emergent SAE									
Subjects < 65 years of age	1972	769 (39.0)	22.6	2051	856 (41.7)	24.6	4023	1625 (40.4)	23.6
Subjects ≥ 65 years of age	1260	600 (47.6)	30.1	1209	625 (51.7)	31.1	2469	1225 (49.6)	30.6
Discontinuations or interruptions due to an adverse event									
Subjects < 65 years of age	1972	232 (11.8)	6.8	2051	218 (10.6)	6.3	4023	450 (11.2)	6.5
Subjects ≥ 65 years of age	1260	235 (18.7)	11.8	1209	198 (16.4)	9.8	2469	433 (17.5)	10.8

%PY = patients with at least 1 emergent adverse event per 100 patient-years.
The subgroup of subjects with a baseline HR ≥70 bpm corresponds to the overall study population.
N = the number of subjects in the treatment group; n = number of subjects reporting at least 1 occurrence; % = n/N * 100; PY = patient-years; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Source: CL3-063, post hoc analyses: NP32844, p. 1260, 1268, 1310, 1323, 1403, 1412, 1450, 1464.

There were no meaningful differences in adverse events in subgroup analysis by gender. The subgroup analysis by race was limited because there were very few non-Caucasians.

Table 76. Applicant's analysis of adverse events by race - SHIFT

	Ivabradine			Placebo			Total		
	N	n (%)	%PY	N	n (%)	%PY	N	n (%)	%PY
Subjects with a TEAE									
Caucasian subjects	2872	2186 (76.1)	44.1	2889	2157 (74.7)	42.9	5761	4343 (75.4)	43.5
Non-Caucasian subjects	360	228 (63.3)	50.8	371	235 (63.3)	50.9	731	463 (63.3)	50.9
Subjects with a treatment-emergent SAE									
Caucasian subjects	2872	1272 (44.3)	25.7	2889	1359 (47.0)	27.0	5761	2631 (45.7)	26.4
Non-Caucasian subjects	360	97 (26.9)	21.6	371	122 (32.9)	26.5	731	219 (30.0)	24.1

%PY = patients with at least 1 emergent adverse event per 100 patient-years. Non-Caucasian includes: asian, black and subjects classified as other.
N = the number of subjects in the treatment group; n = number of subjects reporting at least 1 occurrence; % = n/N * 100; PY = patient-years; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Source: CL3-063, Additional post-hoc analyses - Safety, Table 9 to Table 12, Module 5.3.5.3.

7.5.4 Drug-Disease Interactions

These were discussed in Clinical Pharmacology. There was minimal impact of severe renal impairment and of mild to moderate hepatic impairment on the PK and PD of ivabradine.

The applicant's analysis of adverse events based on heart failure etiology, baseline LVEF, baseline NYHA class, and baseline eGFR found that there was generally a higher incidence of

events in subgroups with more severe disease characteristics (i.e., LVEF ≤ 15%, NYHA Class IV, eGFR < 60 mL/min) in both treatment groups. The applicant concluded that there were no important differences in the ivabradine safety profile between subgroups of subjects, and no important differences in preferred terms between subgroups of subjects. (Source: CSR NP32844)

Table 77. Applicant's analysis of adverse events by ischemic heart failure - SHIFT

	Ivabradine			Placebo			Total		
	N	n (%)	%PY	N	n (%)	%PY	N	n (%)	%PY
Subjects with a TEAE									
Ischemic heart failure	2208	1666 (75.5)	44.7	2199	1610 (73.2)	42.7	4407	3276 (74.3)	43.7
Non-ischemic heart failure	1024	748 (73.1)	44.7	1061	782 (73.7)	45.3	2085	1530 (73.4)	45.0
Deaths									
Ischemic heart failure	2208	369 (16.7)	9.0	2199	401 (18.2)	9.9	4407	770 (17.5)	9.5
Non-ischemic heart failure	1024	141 (13.8)	7.6	1061	163 (15.4)	8.8	2085	304 (14.6)	8.2
Subjects with a treatment-emergent SAE									
Ischemic heart failure	2208	983 (44.5)	26.4	2199	1035 (47.1)	27.5	4407	2018 (45.8)	26.9
Non-ischemic heart failure	1024	386 (37.7)	23.0	1061	446 (42.0)	25.9	2085	832 (39.9)	24.5
Discontinuations or interruptions due to an adverse event									
Ischemic heart failure	2208	320 (14.5)	8.6	2199	276 (12.6)	7.3	4407	596 (13.5)	8.0
Non-ischemic heart failure	1024	147 (14.4)	8.8	1061	140 (13.2)	8.1	2085	287 (13.8)	8.4

%PY = patients with at least 1 emergent adverse event per 100 patient-years.
The subgroup of subjects with a baseline HR ≥70 bpm corresponds to the overall study population.
N = the number of subjects in the treatment group; n = number of subjects reporting at least 1 occurrence; % = n/N * 100; PY = patient-years; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Source: CL3-063, post hoc analyses: NP32844, p. 712, p. 722, p. 766, p. 781, p. 865, p. 871, p. 901, p. 911.

Table 78. Applicant's analysis of adverse events by NYHA Class - SHIFT

	Ivabradine			Placebo			Total		
	N	n (%)	%PY	N	n (%)	%PY	N	n (%)	%PY
Subjects with a TEAE									
Class II	1579	1166 (73.8)	43.1	1581	1149 (72.7)	41.9	3160	2315 (73.3)	42.5
Class III or IV	1652	1247 (75.5)	46.3	1678	1242 (74.0)	45.2	3330	2489 (74.7)	45.7
Class IV	50	40 (80.0)	64.6	61	52 (85.3)	70.3	111	92 (82.9)	67.7
Deaths									
Class II	1579	197 (12.5)	6.7	1581	211 (13.4)	7.2	3160	408 (12.9)	7.0
Class III or IV	1652	313 (19.0)	10.5	1678	352 (21.0)	11.8	3330	665 (20.0)	11.1
Class IV	50	18 (36.0)	27.7	61	30 (49.2)	36.5	111	48 (43.2)	32.6
Subjects with a treatment-emergent SAE									
Class II	1579	601 (38.1)	22.2	1581	643 (40.7)	23.4	3160	1244 (39.4)	22.8
Class III or IV	1652	767 (46.4)	28.5	1678	837 (49.9)	30.4	3330	1604 (48.2)	29.5
Class IV	50	29 (58.0)	46.9	61	42 (68.9)	56.8	111	71 (64.0)	52.2
Discontinuations or interruptions due to an adverse event									
Class II	1579	204 (12.9)	7.5	1581	171 (10.8)	6.2	3160	375 (11.9)	6.9
Class III or IV	1652	263 (15.9)	9.8	1678	245 (14.6)	8.9	3330	508 (15.3)	9.3
Class IV	50	10 (20.0)	16.2	61	9 (14.8)	12.2	111	19 (17.1)	14.0

%PY = patients with at least 1 emergent adverse event per 100 patient-years.
The subgroup of subjects with a baseline HR ≥70 bpm corresponds to the overall study population.
N = the number of subjects in the treatment group; n = number of subjects reporting at least 1 occurrence; % = n/N * 100; PY = patient-years; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Source: CL3-063, post hoc analyses: NP32844, p. 306, p. 314, p. 353, p. 365, p. 445, p. 454, p. 492, p. 505, p. 580, p. 582, p. 588, p. 590.

7.5.5 Drug-Drug Interactions

Pharmacokinetic drug interactions were described in Clinical Pharmacology. The reviewer's recommendations regarding labeling will be filed in a separate addendum. The applicant analyzed

the SHIFT data by beta-blocker intake at randomization, % beta-blocker dose at target, and amiodarone intake at randomization.

The applicant's analysis showed that subjects taking a beta-blocker at baseline had less treatment emergent adverse events (TEAE), SAE, and deaths. There was also a trend of fewer TEAE, SAEs, and deaths as subjects were taking closer to the target dose of ESC recommended beta-blockers. (source: applicant's Summary of Clinical Safety, Table 52).

With respective to subjects taking amiodarone, the overall rate of TEAE leading to drug withdrawal in subjects on amiodarone at baseline and ivabradine was higher than that in placebo. The rate for overall TEAE was similar between arms. The table below highlights were the rate in the ivabradine group was higher than the placebo group. The rate for SAE was worse in the placebo arm. The rates generally appear higher for adverse events of concern, however it is difficult to conclude too much from these data because there was very little amiodarone use in SHIFT (84 ivabradine , 104 placebo).

Table 79. Adverse events in subjects taking amiodarone at baseline – SHIFT on treatment

	Ivabradine N=84 132.5 PY		Placebo N=104 168.7 PY	
	%	%PY	%	%PY
TEAE leading to drug withdrawal	32.1	20.4	15.4	9.5
Cardiac arrhythmias	16.7	10.6	3.9	2.4
Atrial fibrillation	8.3	5.3	2.9	1.8
Atrial flutter	3.4	2.3	0	0
Sick sinus syndrome	2.4	1.5	0	0
Eye disorders	3.6	2.3	0	0
TEAE	81.0	51.3	81.7	50.4
Cardiac arrhythmias	34.5	21.9	21.2	13.0
Supraventricular arrhythmias	26.2	16.6	10.6	6.5
Eye disorders	13.1	8.3	4.8	3.0
SAEs	56.0	35.5	63.5	39.1

Adapted from applicant's Table 13, 14, 15 from Additional post-hoc analyses – safety

Reviewer comment: Loop diuretics

The Cross Disciplinary Team Leader, Dr, Marciniak, has performed some post hoc logistic regression analyses of the PCE and its components. He has found a strong association between the use of loop diuretics and CV mortality. The safety reviewer has confirmed his analysis and agrees that there is a strong association; however the nominal p-values are descriptive without adjustment of multiplicity. The association is that the treatment effect in the ivabradine group + loop diuretic is different from the treatment effect in the placebo+ loop diuretic group. It does not confirm that loop diuretics and ivabradine are more effective than loop diuretics and placebo. In addition, there is not a plausible biologic mechanism for this interaction. Most subjects taking loop diuretic were taking furosemide.

Furosemide is an OAT3 substrate. There is no evidence that ivabradine or its major metabolite is affected by OAT3. The reviewer believes that subjects taking loop diuretics identifies a more advanced symptomatic heart failure and have higher risk for cardiovascular events, and so these patients are likely to derive more benefit from treatments.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

7.6.2 Human Reproduction and Pregnancy Data

Data are limited in humans. Pregnancy was reported in 3 subjects, aged 23-27 years old, treated with ivabradine.

- One subject was in the SHIFT trial and she chose to terminate the pregnancy early.
- One subject took ivabradine for 3 days (total cumulative dose, 50 mg). She discovered the pregnancy on Day 9 (pregnancy test was negative on Day 0) and withdrew from the study. She carried the baby to full-term, had a live birth with no identified dysmorphic features.
- One subject had a positive pregnancy test at inclusion, but was mistakenly randomized. She received a total of 30 mg, and was withdrawn from the study on Day 2. The report did not say how far along the pregnancy was. She carried the baby to full-term, had a live birth with no identified dysmorphic features.

Preclinical data clearly show that ivabradine is a teratogen that causes malformations in the heart. The reviewer thinks that it should not be used in women of child-bearing potential who are not using appropriate contraceptive measures.

Post marketing data

Since the first marketing authorization in 2005 up to October 2013, a total of 16 cases of pregnancy were reported. All took the drug during the first trimester. 1/9 live births took the drug during the third trimester after a break during the second trimester.

- 2/16 induced abortions
- 5/16 were lost to follow-up, but 1 subject had a normal ECHO at week 22. 2 took drug until the 2nd trimester.
- 9/16 had live births. Normal babies although 2 were premature - growth retardation (a) , growth restriction (b))
  a. Delivery was induced due to harmonious in utero fetal growth retardation (37.7 weeks of amenorrhea, 2510 g, height 46 cm, cranial perimeter 30.5 cm). Mother with aortic valvular insufficiency, Marfan's syndrome, smoker, also taking metoprolol, aspirin cardio, enoxaparin, and pantoprazole.
  b. At 34 weeks of pregnancy, biometric fetal parameters were not growing. C-section at 36 weeks, birth weight 2120 g. No malformation reported.

In the European SmPC, ivabradine is contraindicated in women of child-bearing potential who are not using appropriate contraceptive measures.

7.6.3 Pediatrics and Assessment of Effects on Growth

Safety in this population has not been established. (b) (4)

[redacted]

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

An overdose was reported in 2 patients treated with ivabradine in SHIFT. Subject 063 458 5003 06697 experienced dizziness and tinnitus. This was a 37 year old male who was also taking furosemide, spironolactone, metformin and glibenamide. For ~ 6 days he doubled his dose to 10 mg BID, which was when he felt his symptoms. It is noted that loop diuretics can also cause tinnitus. In terms of a possible potentiation of effect, furosemide is an OAT3 substrate. There is no evidence that ivabradine or its metabolite affects OAT3. Subject 063 752 2525 00328 had no symptoms despite taking ~ 15 mg BID.

No rebound was observed in several dedicated studies. See **6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects.**

7.7 Additional Submissions / Safety Issues

8 Postmarket Experience

Ivabradine has been approved since 2005. The postmarking experience is generally similar to the data seen in the clinical trials. Uncommon adverse reactions (incidence ≥ 1/1000 to < 1/100) include eosinophilia, hyperuricemia, vertigo, palpitations, supraventricular extra systoles, dyspnea, nausea, constipation, diarrhea, muscle cramps, elevated creatinine in blood, and ECG prolonged QT interval. These events were observed in the clinical trials, but the most frequent spontaneous reports are related to dyspnea, dizziness, nausea, palpitations, headache, atrial fibrillation, diarrhea, ventricular extra systoles, muscle spasms and vertigo.

Most of the new adverse events added to the EU label occurred in the setting of bradycardia. They include hypotension, malaise, syncope, asthenia, fatigue.

Angioedema and urticaria have also been reported and added to the EU label. These cases occurred in patients with a medical history of hypersensitivity or in association with concomitant drugs known for hypersensitivity reactions. Most of the cases of angioedema were reported as serious events; evolution was favorable with symptomatic treatment and withdrawal of ivabradine; there was no fatal outcome.

The occurrence of postmarketing cases of diplopia, and visual impairment were also added as new undesirable effects. See Section **7.6.2 Human Reproduction and Pregnancy Data** for information on pregnancy.

9 Appendices

9.1 Literature Review/References

See foot notes.

9.2 Labeling Recommendations

These will be written in an amendment to this review.

9.3 Advisory Committee Meeting

A meeting is scheduled for January 14, 2015.

9.4 SHIFT-HF Committee Members and Contract Research Organizations

The Executive Committee was co-chaired b (b) (4) Members of the EC included J (b) (4)

The chair of the Steering Committee was (b) (4) The Chair of the Endpoint Validation Committee was (b) (4) The Chair of the Data Monitoring Committee was (b) (4)

(b) (4) was in charge of the IV/WRS. (b) (4) was in charge of endpoint data management. (b) (4)) was in charge of the e-CRF software site setup, conduct, and closure. Six different CROs were responsible for the local site management of the study.

9.5 SHIFT Adjudication endpoint definitions

1. Hospitalisations

Hospitalisation is defined as any attendance at hospital requiring completion of the hospital admission procedures and/or at least an overnight stay or until death of the patient.

Accordingly, in most cases, the date of entry and the date of discharge will be different. An event leading to the prolongation of an ongoing hospitalisation, with or without the transfer of the patient in a specialised hospital department, will be considered as an hospitalisation. The adjudication process will specify if the hospitalisation is considered as planned or unplanned. An hospitalisation will be considered as unplanned when triggered by a clinical event (e.g.: worsening of the considered disease,...). An unplanned hospitalisation can be delayed from the causal event.

1.1. Cardiovascular hospitalization

1.1.1. Hospitalisation for worsening Heart Failure

- Patient should be hospitalised (see definition above).
- New or increasing symptoms of heart failure (including dyspnoea, fatigue, ...)
- And new or increasing signs of heart failure including signs of fluid retention (such as pulmonary rales, peripheral oedema, raised jugular venous pressure, weight gain,...), or objective evidence of heart failure (such as for instance pulmonary oedema/congestion in chest X ray,)
- and a significant change in the treatment to improve heart failure defined by: initiation of intravenous diuretics or other intravenous medications (excluding cardiac glycosides) or mechanical ventilation or mechanical support (intra-aortic balloon pump, ventricular assist device).

Patient with cardiogenic shock will fulfil the definition of HF.

In presence of the criteria listed above, heart failure will be adjudicated even in presence of other causes for hospital admission, related or not with the episode of worsening heart failure: e.g.: pneumonia, anaemia, atrial fibrillation.

In case of concomitant occurrence of myocardial infarction and worsening heart failure, the cause considered by EVC members as being the main reason for hospital admission will be adjudicated (see 11.3).

Planned or unplanned hospitalisation for heart transplant will be adjudicated as unplanned hospitalisation for worsening heart failure.

1.1.2. Hospitalisation for Myocardial Infarction

- Patient should be hospitalised (see definition above).
- A diagnosis of MI will be made if a typical elevation of biochemical markers of myocardial necrosis, exceeding the MI decision limit given by the hospitals were the patients will be hospitalised, [troponin, creatine kinase (CK), MB fraction of CK (CK-MB) or, when exceptionally unavailable, aspartate amino-transferase (AST) or myoglobin] are observed with at least one of the following:

__ischaemic symptoms *i.e.* cardiac ischaemic type pain lasting at least 20 minutes or pulmonary oedema or cardiogenic shock not otherwise explained;

__development of pathologic Q waves on the ECG (_ 0.03 second in duration) in at least two consecutive ECG leads not present on an ECG recorded before the current event;

__ECG changes indicative of ischaemia (transient ST segment elevation or depression or
new left bundle branch block);

__coronary artery intervention (*e.g.* coronary angioplasty).
All confirmed MI will be counted as events, whether they occurred spontaneously or as a direct consequence of an investigational procedure or operation.

1.1.3. Other Cardiovascular hospitalisation

Hospitalisations must be caused by a fully documented cardiovascular cause (excepted hospitalisation from heart failure and hospitalisation from MI)- for example, unstable angina, stroke, arrhythmia, hospitalisation related to a vascular procedure/operation, ruptured aneurysm, pulmonary embolism, hypotension, syncope, hypertensive emergency, …
Working definitions for the main cardiovascular events will be detailed in a specific document.

1.2. Non Cardiovascular hospitalisation

Hospitalisation will be considered non-cardiovascular only if an unequivocal and documented non-cardiovascular cause can be established.

1.3. Hospitalisation for undetermined cause

This will correspond to hospitalisations for which it is not possible to specify whether they are cardiovascular or not.
At the time of the final statistical analysis, hospitalisation of undetermined cause will be considered as cardiovascular hospitalisation.

2.0 Deaths

The EVC members must adjudicate the PSE according to the cause of death. For cardiovascular and unknown causes, the mode of death must be also specified.

2.1. Cause of death

2.1.1. All cause deaths

This will consist of all deaths:
- cardiovascular deaths,
- non cardiovascular deaths,
- deaths of unknown cause.

2.1.2. Cardiovascular deaths

A cardiovascular death will be defined as:
(i) Death due to heart failure, death due to myocardial infarction (MI), arrhythmic death or presumed arrhythmic death
(ii) Other cardiovascular death – for example, a stroke, ruptured aneurysm, or pulmonary embolism.
Working definitions for the main cardiovascular events will be detailed in a specific document.

2.1.2.1. Death from Heart Failure

Death occurring from worsening or uncontrolled heart failure:
- with or without hospitalisation,
- and heart failure is considered a major factor leading to death,
- even if the terminal event is an arrhythmia and unless there is an obvious other cause for the death.

2.1.2.2. Death from Myocardial Infarction

Death occurring up to 28 days after a documented MI (refer to the description of MI in paragraph 11.1.1.2):
- with or without hospitalisation,
- even if the terminal event is an arrhythmia and unless there is an obvious other cause for the death.

2.1.2.3. Arrhythmic death or presumed arrhythmic death

A death will be classified as arrhythmic death or presumed arrhythmic death if it is a sudden
death and in case of:

- electrical evidence for the occurrence of a ventricular arrhythmia,
- or witnessed sudden unexpected collapse,
- or unwitnessed death within 24 hours from last known vital status and in the absence of obvious ongoing worsening heart failure, acute myocardial infarction or other cause of death unless the death is considered as related to ongoing worsening of heart failure (refer to 11.2.1.2.1) or to a MI (refer to 11.2.1.2.2) or other obvious cause of death.

2.1.2.4. Death from other cardiovascular causes

Death must be caused by a fully documented cardiovascular cause (excepted death from heart failure and death from MI) for example, stroke, pulmonary embolism, ruptured aortic aneurysm.

2.1.3. Non-cardiovascular deaths

Deaths will be considered non-cardiovascular only if an unequivocal and documented noncardiovascular cause can be established (e.g.: renal failure, cancer, respiratory failure, trauma, infection, suicide,...).

2.1.4. Death of unknown cause

This will correspond to non violent or traumatic deaths for which it is not possible to specify whether they are cardiovascular or not.

At the time of the final statistical analysis, death of unknown cause will be considered as cardiovascular death.

2.2. Mode of death

For deaths of unknown cause and cardiovascular deaths, the mode of death (non sudden death or sudden death):

- sudden death
__witnessed instantaneous unexpected death
__witnessed within 1 hour after the onset of symptoms
__witnessed 1-24 hours after the onset of symptoms
__not witnessed unexpected death, including patient found dead
- non sudden death

will be specified.

Death during sleep will be considered as a "witnessed instantaneous unexpected death".

Witnessed death known to have occurred within 24 hours of the onset of the symptoms but for which it is unknown whether they occurred within 1 hour or 1-24 hours after the onset of the symptoms will be considered as "witnessed 1-24 hours after the onset of symptoms".

3.0 Relationship between clinical events and PSE classification

In case of several causes for a same hospitalisation (same day of hospitalisation), only one cause will be adjudicated. Other(s) cause(s) will be rejected (for worsening heart failure see 11.1.1.1).

In case of concomitant occurrence of a MI and a worsening HF (same day of hospitalisation), the cause considered as being the main reason for hospital admission will be adjudicated if the definition is fulfilled. During a same hospitalisation two clinical events can occur, the second clinical event being considered as a reason for a prolongation of hospitalisation. These two clinical events will represent 2 PSE. They should be adjudicated separately with their respective date of occurrence which could be either the date of hospitalisation, the date of transfer to the cardiology department if any, or the date of diagnosis.

In case of hospitalisation for a MI followed by the occurrence of worsening HF (different date of occurrence), a second PSE should be taken into account (hospitalisation for MI + prolongation of hospitalisation for worsening HF).

In case of prolongation of hospitalisation for worsening HF in patients already hospitalized for a non cardiovascular reason, 2 PSE should be taken into account (hospitalisation for non cardiovascular reason + hospitalisation for worsening HF).

In case of death occurring in a context of worsening HF with concomitance of another cardiovascular cause (e.g. within 28 days from MI), or non cardiovascular cause (e.g.: pneumopathy…), the PSE will be classified as death from HF.
In case of hospitalisation followed by a death, 2 PSE should be taken into account (hospitalisation + death).

9.6 Additional adverse event analyses

The tables in this section are sorted in descending order by percent of subjects in the ivabradine arm experiencing the adverse event in the SHIFT trial.

Table 80. SAE (includes fatal) by preferred term (≥ 0.5% of ivabradine treated subjects) – SHIFT on treatment

	Ivabradine N=3260			Placebo N=3278				
Preferred Term	**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**	
All	1371	(42.1)	25.3	1479	(45.1)	26.8	0.93	(0.88, 0.98)
Cardiac failure	508	(15.6)	9.4	663	(20.2)	12.0	0.77	(0.69, 0.86)
Atrial fibrillation	126	(3.9)	2.3	106	(3.2)	1.9	1.20	(0.93, 1.55)
Angina unstable	113	(3.5)	2.1	119	(3.6)	2.2	0.95	(0.74, 1.22)
Sudden death	111	(3.4)	2.0	119	(3.6)	2.2	0.94	(0.73, 1.21)
Pneumonia	70	(2.1)	1.3	65	(2.0)	1.2	1.08	(0.77, 1.51)
Sudden cardiac death	73	(2.2)	1.3	68	(2.1)	1.2	1.08	(0.78, 1.50)
Acute myocardial infarction	63	(1.9)	1.2	53	(1.6)	1.0	1.20	(0.84, 1.72)
Myocardial infarction	57	(1.7)	1.1	51	(1.6)	0.9	1.12	(0.77, 1.63)
Angina pectoris	51	(1.6)	0.9	55	(1.7)	1.0	0.93	(0.64, 1.36)
Chronic obstructive pulmonary disease	35	(1.1)	0.6	33	(1.0)	0.6	1.07	(0.67, 1.72)
Ischaemic stroke	34	(1.0)	0.6	46	(1.4)	0.8	0.74	(0.48, 1.15)
Ventricular tachycardia	31	(1.0)	0.6	46	(1.4)	0.8	0.68	(0.43, 1.07)
Cardiovascular evaluation	27	(0.8)	0.5	27	(0.8)	0.5	1.01	(0.59, 1.72)
Acute pulmonary oedema	20	(0.6)	0.4	25	(0.8)	0.5	0.80	(0.45, 1.44)
Arteriogram coronary	24	(0.7)	0.4	12	(0.4)	0.2	2.01	(1.01, 4.01)
Atrial flutter	22	(0.7)	0.4	19	(0.6)	0.3	1.16	(0.63, 2.14)
Cardiac resynchronisation therapy	20	(0.6)	0.4	29	(0.9)	0.5	0.69	(0.39, 1.22)
Diabetes mellitus inadequate control	23	(0.7)	0.4	33	(1.0)	0.6	0.70	(0.41, 1.19)
Ventricular fibrillation	20	(0.6)	0.4	11	(0.3)	0.2	1.83	(0.88, 3.81)
Blood pressure inadequately controlled	17	(0.5)	0.3	13	(0.4)	0.2	1.31	(0.64, 2.69)

	Ivabradine N=3260			Placebo N=3278				
Preferred Term	**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**	
Bradycardia	15	(0.5)	0.3	2	(0.1)	0.0	7.54	(1.73, 32.95)
Cardiac failure congestive	17	(0.5)	0.3	19	(0.6)	0.3	0.90	(0.47, 1.73)
Cardiogenic shock	15	(0.5)	0.3	16	(0.5)	0.3	0.94	(0.47, 1.90)
Implantable defibrillator insertion	17	(0.5)	0.3	21	(0.6)	0.4	0.81	(0.43, 1.53)
Peripheral arterial occlusive disease	15	(0.5)	0.3	15	(0.5)	0.3	1.01	(0.49, 2.06)
Ventricular extra systoles	15	(0.5)	0.3	9	(0.3)	0.2	1.68	(0.74, 3.83)

Reviewer's analysis: SHIFT\ data\ae\LD2d\serious\LD2dser_fatal_bytx
By actual treatment received

Table 81. Non-fatal SAE- SHIFT and BEAUTIFUL

	SHIFT								BEAUTIFUL							
	Ivabradine N=3260			Placebo N=3278					Ivabradine N=5477			Placebo N=5430				
AE	n	%	%PY	n	%	%PY	RR	(95% CI)	n	%	%PY	n	%	%PY	RR	(95% CI)
All	1146	(35.2)	21.1	1264	(38.6)	22.9	0.91	(0.85, 0.97)	1357	(24.8)	18.7	1519	(28.0)	18.7	0.89	(0.84, 0.95)
CHF or pulmonary edema	500	(15.3)	9.2	637	(19.4)	11.6	0.79	(0.71, 0.88)	397	(7.2)	5.5	432	(8.0)	5.3	0.91	(0.80, 1.04)
CHF	493	(15.1)	9.1	624	(19.0)	11.3	0.79	(0.71, 0.88)	397	(7.2)	5.5	432	(8.0)	5.3	0.91	(0.80, 1.04)
Arrhythmia	217	(6.7)	4.0	191	(5.8)	3.5	1.14	(0.94, 1.38)	234	(4.3)	3.2	243	(4.5)	3.0	0.95	(0.80, 1.13)
Supraventricular	150	(4.6)	2.8	129	(3.9)	2.3	1.17	(0.93, 1.47)	160	(2.9)	2.2	165	(3.0)	2.0	0.96	(0.77, 1.19)
AF or AFL	143	(4.4)	2.6	125	(3.8)	2.3	1.15	(0.91, 1.45)	158	(2.9)	2.2	157	(2.9)	1.9	1.00	(0.80, 1.24)
Atrial fibrillation	125	(3.8)	2.3	106	(3.2)	1.9	1.19	(0.92, 1.53)	126	(2.3)	1.7	133	(2.4)	1.6	0.94	(0.74, 1.20)
Atrial flutter	22	(0.7)	0.4	19	(0.6)	0.3	1.16	(0.63, 2.14)	35	(0.6)	0.5	28	(0.5)	0.3	1.24	(0.76, 2.04)
Ventricular arrhythmia	54	(1.7)	1.0	67	(2.0)	1.2	0.81	(0.57, 1.16)	47	(0.9)	0.6	72	(1.3)	0.9	0.65	(0.45, 0.94)
Ventricular tachycardia	30	(0.9)	0.6	46	(1.4)	0.8	0.66	(0.42, 1.04)	26	(0.5)	0.4	53	(1.0)	0.7	0.49	(0.31, 0.78)
Ventricular fibrillation	9	(0.3)	0.2	8	(0.2)	0.1	1.13	(0.44, 2.93)	8	(0.1)	0.1	8	(0.1)	0.1	0.99	(0.37, 2.64)
Sick sinus syndrome	5	(0.2)	0.1	.		.	.	-	7	(0.1)	0.1	2	(0.0)	0.0	3.47	(0.72, 16.70)
Tachycardia	27	(0.8)	0.5	23	(0.7)	0.4	1.18	(0.68, 2.05)	38	(0.7)	0.5	37	(0.7)	0.5	1.02	(0.65, 1.60)
PVCs (ventricular extra systoles)	15	(0.5)	0.3	9	(0.3)	0.2	1.68	(0.74, 3.83)	10	(0.2)	0.1	9	(0.2)	0.1	1.10	(0.45, 2.70)
Bradycardia, HR decreased	18	(0.6)	0.3	2	(0.1)	0.0	9.05	(2.10, 38.9)	29	(0.5)	0.4	6	(0.1)	0.1	4.79	(1.99, 11.53)
Heart rate decreased	3	(0.1)	0.1						7	(0.1)	0.1					
Bradycardia	15	(0.5)	0.3	2	(0.1)	0.0	7.54	(1.73, 32.9)	22	(0.4)	0.3	6	(0.1)	0.1	3.64	(1.48, 8.97)
Syncope	13	(0.4)	0.2	23	(0.7)	0.4	0.57	(0.29, 1.12)	21	(0.4)	0.3	27	(0.5)	0.3	0.77	(0.44, 1.36)

	SHIFT								BEAUTIFUL							
	Ivabradine N=3260			Placebo N=3278					Ivabradine N=5477			Placebo N=5430				
AE	n	%	%PY	n	%	%PY	RR (95% CI)		n	%	%PY	n	%	%PY	RR (95% CI)	
Torsade de Pointes	2	(0.1)	0.0	.		.	.	-	.		.	.		.	.	
cardiogenic shock	7	(0.2)	0.1	4	(0.1)	0.1	1.76	(0.52, 6.01)	.		.	1	(0.0)	0.0	.	-
CAD, myocardial ischemia	187	(5.7)	3.4	199	(6.1)	3.6	0.94	(0.77, 1.14)	277	(5.1)	3.8	342	(6.3)	4.2	0.80	(0.69, 0.93)
ACS (AMI and unstable angina)	179	(5.5)	3.3	190	(5.8)	3.4	0.95	(0.78, 1.16)	263	(4.8)	3.6	325	(6.0)	4.0	0.80	(0.68, 0.94)
Acute MI	73	(2.2)	1.3	80	(2.4)	1.5	0.92	(0.67, 1.26)	108	(2.0)	1.5	126	(2.3)	1.5	0.85	(0.66, 1.10)
Angina (includes USA, angina pectoris)	159	(4.9)	2.9	170	(5.2)	3.1	0.94	(0.76, 1.16)	186	(3.4)	2.6	255	(4.7)	3.1	0.72	(0.60, 0.87)
Unstable angina	112	(3.4)	2.1	118	(3.6)	2.1	0.95	(0.74, 1.22)	152	(2.8)	2.1	194	(3.6)	2.4	0.78	(0.63, 0.96)
Angina pectoris	51	(1.6)	0.9	55	(1.7)	1.0	0.93	(0.64, 1.36)	37	(0.7)	0.5	66	(1.2)	0.8	0.56	(0.38, 0.84)
Infection, all	182	(5.6)	3.4	200	(6.1)	3.6	0.92	(0.76, 1.12)	178	(3.2)	2.5	186	(3.4)	2.3	0.95	(0.78, 1.16)
pneumonia	79	(2.4)	1.5	72	(2.2)	1.3	1.10	(0.80, 1.51)	78	(1.4)	1.1	76	(1.4)	0.9	1.02	(0.75, 1.40)
Stroke, ICH, TIA	56	(1.7)	1.0	73	(2.2)	1.3	0.77	(0.55, 1.09)	95	(1.7)	1.3	101	(1.9)	1.2	0.93	(0.70, 1.23)
Stroke (ischemic, hemorrhagic)	46	(1.4)	0.8	59	(1.8)	1.1	0.78	(0.53, 1.14)	73	(1.3)	1.0	76	(1.4)	0.9	0.95	(0.69, 1.31)
Ischemic stroke	32	(1.0)	0.6	51	(1.6)	0.9	0.63	(0.41, 0.98)	41	(0.7)	0.6	50	(0.9)	0.6	0.81	(0.54, 1.22)
TIA	11	(0.3)	0.2	12	(0.4)	0.2	0.92	(0.41, 2.08)	18	(0.3)	0.2	26	(0.5)	0.3	0.69	(0.38, 1.26)
Systemic embolism	2	(0.1)	0.0	4	(0.1)	0.1	0.50	(0.09, 2.73)	.		.	.		.	.	
solid neoplasia, ALL (benign, malignant, unknown)	50	(1.5)	0.9	46	(1.4)	0.8	1.09	(0.73, 1.62)	72	(1.3)	1.0	81	(1.5)	1.0	0.88	(0.64, 1.21)
cancer (non-squamous cell)	34	(1.0)	0.6	32	(1.0)	0.6	1.07	(0.66, 1.73)	53	(1.0)	0.7	63	(1.2)	0.8	0.83	(0.58, 1.19)
COPD, COPD exacerbation	37	(1.1)	0.7	35	(1.1)	0.6	1.06	(0.67, 1.68)	28	(0.5)	0.4	32	(0.6)	0.4	0.87	(0.52, 1.44)

	SHIFT								BEAUTIFUL							
	Ivabradine N=3260			Placebo N=3278					Ivabradine N=5477			Placebo N=5430				
AE	n	%	%PY	n	%	%PY	RR (95% CI)		n	%	%PY	n	%	%PY	RR (95% CI)	
bleeding	31	(1.0)	0.6	28	(0.9)	0.5	1.11	(0.67, 1.85)	26	(0.5)	0.4	21	(0.4)	0.3	1.23	(0.69, 2.18)
elevated BUN or Cr, anuria, ARF, CRF, oliguria	29	(0.9)	0.5	27	(0.8)	0.5	1.08	(0.64, 1.82)	33	(0.6)	0.5	25	(0.5)	0.3	1.31	(0.78, 2.20)
Renal failure acute	11	(0.3)	0.2	7	(0.2)	0.1	1.58	(0.61, 4.07)	14	(0.3)	0.2	4	(0.1)	0.0	3.47	(1.14, 10.54)
diabetes, glucose intolerance, hyperglycemia, HbA1c, glycosuria, insulin resistance	29	(0.9)	0.5	36	(1.1)	0.7	0.81	(0.50, 1.32)	30	(0.5)	0.4	28	(0.5)	0.3	1.06	(0.63, 1.77)
Conduction disturbance	25	(0.8)	0.5	11	(0.3)	0.2	2.29	(1.13, 4.65)	21	(0.4)	0.3	21	(0.4)	0.3	0.99	(0.54, 1.81)
AV block	24	(0.7)	0.4	10	(0.3)	0.2	2.41	(1.15, 5.03)	18	(0.3)	0.2	18	(0.3)	0.2	0.99	(0.52, 1.90)
Complete or third degree AV block	17	(0.5)	0.3	4	(0.1)	0.1	4.27	(1.44, 12.6)	10	(0.2)	0.1	11	(0.2)	0.1	0.90	(0.38, 2.12)
Atrioventricular block 2nd degree	7	(0.2)	0.1	4	(0.1)	0.1	1.76	(0.52, 6.01)	8	(0.1)	0.1	7	(0.1)	0.1	1.13	(0.41, 3.11)
Hypertension, BP increased	26	(0.8)	0.5	21	(0.6)	0.4	1.24	(0.70, 2.20)	28	(0.5)	0.4	23	(0.4)	0.3	1.21	(0.70, 2.10)
stone, renal colic	6	(0.2)	0.1	2	(0.1)	0.0	3.02	(0.61, 14.95)	4	(0.1)	0.1	4	(0.1)	0.0	0.99	(0.25, 3.96)
pancreatitis	8	(0.2)	0.1	6	(0.2)	0.1	1.34	(0.47, 3.86)	5	(0.1)	0.1	4	(0.1)	0.0	1.24	(0.33, 4.62)
glaucoma	3	(0.1)	0.1	1	(0.0)	0.0	3.02	(0.31, 29.0)	2	(0.0)	0.0	2	(0.0)	0.0	0.99	(0.14, 7.03)
cataract	10	(0.3)	0.2	7	(0.2)	0.1	1.44	(0.55, 3.78)	8	(0.1)	0.1	6	(0.1)	0.1	1.32	(0.46, 3.80)
Anaphylactic reaction	1	(0.0)	0.0	.		.	.	(., .)	1	(0.0)	0.0	1	(0.0)	0.0	0.99	(0.06, 15.82)

Red font denotes MedDRA preferred terms. There are small differences in what the applicant reports in their CSR and the reviewer's analysis because the applicant used MedDRA v 7.0 for BEAUTIFUL, included fatal SAE, and they report the results by assigned treatment. For BEAUTIFUL the reviewer used PT that were coded to MedDRA v 9.0 that the applicant had supplied in their adven dataset. Reviewer excludes fatal SAE and reports results by actual treatment. Note that this is not a complete list of all nonfatal SAEs in the trials.
Reviewer's analysis: bs\data\LD2d\create table all, \create table all sponsor2. Applicant's data: SHIFT, BEAUTIFUL\adven

Table 82. Nonfatal SAE by Preferred term (ver 9) occurring ≥0.3%PY ivabradine subjects– SHIFT & BEAUTIFUL

	SHIFT								BEAUTIFUL							
	Ivabradine N=3260			Placebo N=3278					Ivabradine N=5477			Placebo N=5430				
Preferred term	**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**		**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**	
All	1146	(35.2)	21.1	1264	(38.6)	22.9	0.91	(0.85, 0.97)	1357	24.8	18.7	1519	(28.0)	18.7	0.89	(0.84, 0.95)
Cardiac failure	468	(14.4)	8.6	613	(18.7)	11.1	0.77	(0.69, 0.86)	375	(6.8)	5.2	413	(7.6)	5.1	0.90	(0.79, 1.03)
Atrial fibrillation	125	(3.8)	2.3	106	(3.2)	1.9	1.19	(0.92, 1.53)	126	(2.3)	1.7	133	(2.4)	1.6	0.94	(0.74, 1.20)
Angina unstable	112	(3.4)	2.1	118	(3.6)	2.1	0.95	(0.74, 1.22)	152	(2.8)	2.1	194	(3.6)	2.4	0.78	(0.63, 0.96)
Pneumonia	66	(2.0)	1.2	61	(1.9)	1.1	1.09	(0.77, 1.54)	66	(1.2)	0.9	61	(1.1)	0.7	1.07	(0.76, 1.51)
Angina pectoris	51	(1.6)	0.9	55	(1.7)	1.0	0.93	(0.64, 1.36)	37	(0.7)	0.5	66	(1.2)	0.8	0.56	(0.38, 0.84)
Acute myocardial infarction	44	(1.3)	0.8	44	(1.3)	0.8	1.01	(0.67, 1.53)	57	(1.0)	0.8	62	(1.1)	0.8	0.91	(0.64, 1.30)
Chronic obstructive pulmonary disease	34	(1.0)	0.6	33	(1.0)	0.6	1.04	(0.65, 1.67)	21	(0.4)	0.3	24	(0.4)	0.3	0.87	(0.48, 1.56)
Myocardial infarction	31	(1.0)	0.6	37	(1.1)	0.7	0.84	(0.52, 1.35)	52	(0.9)	0.7	66	(1.2)	0.8	0.78	(0.54, 1.12)
Ventricular tachycardia	30	(0.9)	0.6	46	(1.4)	0.8	0.66	(0.42, 1.04)	26	(0.5)	0.4	53	(1.0)	0.7	0.49	(0.31, 0.78)
Cardiovascular evaluation	27	(0.8)	0.5	27	(0.8)	0.5	1.01	(0.59, 1.72)	3	(0.1)	0.0	7	(0.1)	0.1	0.42	(0.11, 1.62)
Ischaemic stroke	25	(0.8)	0.5	38	(1.2)	0.7	0.66	(0.40, 1.09)	30	(0.5)	0.4	39	(0.7)	0.5	0.76	(0.47, 1.22)
Arteriogram coronary	24	(0.7)	0.4	12	(0.4)	0.2	2.01	(1.01, 4.01)	26	(0.5)	0.4	28	(0.5)	0.3	0.92	(0.54, 1.57)
Atrial flutter	22	(0.7)	0.4	19	(0.6)	0.3	1.16	(0.63, 2.14)	35	(0.6)	0.5	28	(0.5)	0.3	1.24	(0.76, 2.04)
Diabetes mellitus inadequate control	23	(0.7)	0.4	33	(1.0)	0.6	0.70	(0.41, 1.19)	26	(0.5)	0.4	25	(0.5)	0.3	1.03	(0.60, 1.78)
Cardiac resynchronisation therapy	20	(0.6)	0.4	29	(0.9)	0.5	0.69	(0.39, 1.22)	2	(0.0)	0.0	1	(0.0)	0.0	1.98	(0.18, 21.8)
Bradycardia	15	(0.5)	0.3	2	(0.1)	0.0	7.54	(1.73, 32.9)	22	(0.4)	0.3	6	(0.1)	0.1	3.64	(1.48, 8.97)
Ventricular extra systoles	15	(0.5)	0.3	9	(0.3)	0.2	1.68	(0.74, 3.83)	10	(0.2)	0.1	9	(0.2)	0.1	1.10	(0.45, 2.70)

	SHIFT								BEAUTIFUL							
	Ivabradine N=3260			Placebo N=3278					Ivabradine N=5477			Placebo N=5430				
Preferred term	n	%	%PY	n	%	%PY	RR (95% CI)		n	%	%PY	n	%	%PY	RR (95% CI)	
Blood pressure inadequately controlled	17	(0.5)	0.3	13	(0.4)	0.2	1.31	(0.64, 2.69)	16	(0.3)	0.2	12	(0.2)	0.1	1.32	(0.63, 2.79)
Cardiac failure congestive	17	(0.5)	0.3	15	(0.5)	0.3	1.14	(0.57, 2.28)	.		.	.		.	.	
Peripheral arterial occlusive disease	15	(0.5)	0.3	15	(0.5)	0.3	1.01	(0.49, 2.06)	17	(0.3)	0.2	28	(0.5)	0.3	0.60	(0.33, 1.09)
Implantable defibrillator insertion	17	(0.5)	0.3	21	(0.6)	0.4	0.81	(0.43, 1.53)	12	(0.2)	0.2	15	(0.3)	0.2	0.79	(0.37, 1.69)
Acute pulmonary oedema	16	(0.5)	0.3	22	(0.7)	0.4	0.73	(0.38, 1.39)	.		.	.		.	.	
Renal failure	14	(0.4)	0.3	13	(0.4)	0.2	1.08	(0.51, 2.29)	13	(0.2)	0.2	14	(0.3)	0.2	0.92	(0.43, 1.96)
Cerebrovascular accident	13	(0.4)	0.2	8	(0.2)	0.1	1.63	(0.68, 3.93)	32	(0.6)	0.4	27	(0.5)	0.3	1.18	(0.71, 1.97)
Syncope	12	(0.4)	0.2	19	(0.6)	0.3	0.64	(0.31, 1.32)	19	(0.3)	0.3	19	(0.3)	0.2	0.99	(0.52, 1.87)

Reviewer's analysis: BEAUTIFUL\LD2d_Bserious. BS\data\ld2d\create table all sponsor 2. spon_pylge0_3.rtf
Occurring in ≥ 0.3%PY ivabradine treated subjects on treatment

Table 83. Common adverse events for which there were some differences between the reviewer's and the applicants in SHIFT or BEAUTIFUL

	SHIFT								BEAUTIFUL							
	Ivabradine N=3260			Placebo N=3278					Ivabradine N=5477			Placebo N=5430				
AE	**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**		**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**	
All	2416	(74.1)	44.5	2390	(72.9)	43.4	1.02	(0.99, 1.05)	3048	(55.7)	42.1	3016	(55.5)	37.0	--	--
CAD, myocardial ischemia	246	(7.5)	4.5	234	(7.1)	4.2	1.06	(0.89, 1.26)	330	(6.0)	4.6	401	(7.4)	4.9	0.82	(0.71, 0.94)
ACS (AMI and unstable angina)	229	(7.0)	4.2	220	(6.7)	4.0	1.05	(0.88, 1.26)	306	(5.6)	4.2	371	(6.8)	4.6	0.82	(0.71, 0.95)
Acute MI	**116**	**(3.6)**	**2.1**	**103**	**(3.1)**	**1.9**	**1.13**	**(0.87, 1.47)**	**147**	**(2.7)**	**2.0**	**166**	**(3.1)**	**2.0**	**0.88**	**(0.71, 1.10)**
Acute MI*	63	(1.9)	1.2	53	(1.6)	1.0	1.20	(0.84, 1.72)	82	(1.5)	1.1	88	(1.6)	1.1	0.92	(0.68, 1.24)
Myocardial infarction*	57	(1.7)	1.1	51	(1.6)	0.9	1.12	(0.77, 1.63)	67	(1.2)	0.9	82	(1.5)	1.0	0.81	(0.59, 1.12)
Cardiac arrest, SCD, sudden death	**186**	**(5.7)**	**3.4**	**188**	**(5.7)**	**3.4**	**0.99**	**(0.81, 1.21)**	**206**	**(3.8)**	**2.8**	**187**	**(3.4)**	**2.3**	**1.09**	**(0.90, 1.32)**
Sudden death*	111	(3.4)	2.0	119	(3.6)	2.2	0.94	(0.73, 1.21)	204	(3.7)	2.8	185	(3.4)	2.3	1.09	(0.90, 1.33)
Sudden cardiac death*	73	(2.2)	1.3	68	(2.1)	1.2	1.08	(0.78, 1.50)	.		.	.		.	.	
Pneumonia	**138**	**(4.2)**	**2.5**	**154**	**(4.7)**	**2.8**	**0.90**	**(0.72, 1.13)**	**147**	**(2.7)**	**2.0**	**133**	**(2.4)**	**1.6**	**1.10**	**(0.87, 1.39)**
Pneumonia*	121	(3.7)	2.2	131	(4.0)	2.4	0.93	(0.73, 1.19)	123	(2.2)	1.7	112	(2.1)	1.4	1.09	(0.85, 1.40)

Reviewer's analysis: bs\data\LD2d\create table cuts. Applicant's data: SHIFT, BEAUTIFUL\adven
Applicant's preferred terms shown in red

Table 84. Adverse events occurring in ≥ 0.5% of subjects in either arm in SHIFT or BEAUTIFUL

	SHIFT								BEAUTIFUL							
	Ivabradine N=3260			Placebo N=3278					Ivabradine N=5477			Placebo N=5430				
Adverse events	**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**		**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**	
All	2416	(74.1)	44.5	2390	(72.9)	43.4	1.02	(0.99, 1.05)	3048	(55.7)	42.1	3016	(55.5)	37.0	--	--
arrhythmia	806	(24.7)	14.9	611	(18.6)	11.1	1.33	(1.21, 1.46)	911	(16.6)	12.6	666	(12.3)	8.2	1.36	(1.24, 1.49)
CHF or pulm edema	742	(22.8)	13.7	887	(27.1)	16.1	0.84	(0.77, 0.91)	585	(10.7)	8.1	615	(11.3)	7.6	0.94	(0.84, 1.05)
CHF	732	(22.5)	13.5	873	(26.6)	15.8	0.84	(0.77, 0.91)	585	(10.7)	8.1	615	(11.3)	7.6	0.94	(0.84, 1.05)
infection, all	646	(19.8)	11.9	740	(22.6)	13.4	0.88	(0.80, 0.97)	754	(13.8)	10.4	835	(15.4)	10.3	0.90	(0.82, 0.99)
supra-ventricular	349	(10.7)	6.4	313	(9.5)	5.7	1.12	(0.97, 1.29)	374	(6.8)	5.2	342	(6.3)	4.2	1.08	(0.94, 1.24)
bradycardia	322	(9.9)	5.9	72	(2.2)	1.3	4.50	(3.50, 5.78)	374	(6.8)	5.2	89	(1.6)	1.1	4.17	(3.32, 5.24)
AF or AFL	296	(9.1)	5.5	247	(7.5)	4.5	1.20	(1.02, 1.41)	332	(6.1)	4.6	304	(5.6)	3.7	1.08	(0.93, 1.26)
hypertension, BP increased	284	(8.7)	5.2	252	(7.7)	4.6	1.13	(0.96, 1.33)	250	(4.6)	3.5	254	(4.7)	3.1	0.98	(0.83, 1.16)
AF	268	(8.2)	4.9	216	(6.6)	3.9	1.25	(1.05, 1.49)	286	(5.2)	4.0	264	(4.9)	3.2	1.07	(0.91, 1.26)
CAD, myocardial ischemia (AMI, ACS)	246	(7.5)	4.5	234	(7.1)	4.2	1.06	(0.89, 1.26)	330	(6.0)	4.6	401	(7.4)	4.9	0.82	(0.71, 0.94)
Angina	242	(7.4)	4.5	257	(7.8)	4.7	0.95	(0.80, 1.12)	281	(5.1)	3.9	350	(6.4)	4.3	0.80	(0.69, 0.93)
diabetes, glucose intolerance, hyperglycemia, HbA1c, glycosuria, insulin resistance	241	(7.4)	4.4	254	(7.7)	4.6	0.95	(0.80, 1.13)	327	(6.0)	4.5	332	(6.1)	4.1	0.98	(0.85, 1.14)
ACS _AMI and unstable angina	229	(7.0)	4.2	220	(6.7)	4.0	1.05	(0.88, 1.26)	306	(5.6)	4.2	371	(6.8)	4.6	0.82	(0.71, 0.95)
ventricular arrhythmia	225	(6.9)	4.1	217	(6.6)	3.9	1.04	(0.87, 1.25)	190	(3.5)	2.6	191	(3.5)	2.3	0.99	(0.81, 1.21)
URI, cold, rhinitis, upper resp tract infection, flu-like illness, sinusitis, sore throat	208	(6.4)	3.8	231	(7.0)	4.2	0.91	(0.76, 1.09)	221	(4.0)	3.1	220	(4.1)	2.7	1.00	(0.83, 1.20)
Cardiac arrest, SCD, asystole, EMD	186	(5.7)	3.4	188	(5.7)	3.4	0.99	(0.81, 1.21)	206	(3.8)	2.8	187	(3.4)	2.3	1.09	(0.90, 1.32)

	SHIFT								BEAUTIFUL							
	Ivabradine N=3260			Placebo N=3278					Ivabradine N=5477			Placebo N=5430				
Adverse events	**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**		**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**	
elevated BUN or Cr, anuria, ARF, CRF, oliguria	179	(5.5)	3.3	212	(6.5)	3.8	0.85	(0.70, 1.03)	202	(3.7)	2.8	180	(3.3)	2.2	1.11	(0.91, 1.35)
infection, viral	149	(4.6)	2.7	154	(4.7)	2.8	0.97	(0.78, 1.21)	133	(2.4)	1.8	153	(2.8)	1.9	0.86	(0.68, 1.08)
PVCs	144	(4.4)	2.7	138	(4.2)	2.5	1.05	(0.84, 1.32)	116	(2.1)	1.6	108	(2.0)	1.3	1.06	(0.82, 1.37)
pneumonia	138	(4.2)	2.5	154	(4.7)	2.8	0.90	(0.72, 1.13)	147	(2.7)	2.0	133	(2.4)	1.6	1.10	(0.87, 1.39)
bronchitis, bronchiolitis, tracheitis, bronchiectasis, lower respiratory tract infection	136	(4.2)	2.5	160	(4.9)	2.9	0.85	(0.68, 1.06)	161	(2.9)	2.2	187	(3.4)	2.3	0.85	(0.69, 1.05)
anemia	124	(3.8)	2.3	137	(4.2)	2.5	0.91	(0.72, 1.15)	94	(1.7)	1.3	96	(1.8)	1.2	0.97	(0.73, 1.29)
acute MI	116	(3.6)	2.1	103	(3.1)	1.9	1.13	(0.87, 1.47)	147	(2.7)	2.0	166	(3.1)	2.0	0.88	(0.71, 1.10)
unstable angina	118	(3.6)	2.2	126	(3.8)	2.3	0.94	(0.73, 1.20)	155	(2.8)	2.1	202	(3.7)	2.5	0.76	(0.62, 0.93)
conduction disturbance	108	(3.3)	2.0	93	(2.8)	1.7	1.17	(0.89, 1.54)	88	(1.6)	1.2	102	(1.9)	1.3	0.86	(0.65, 1.14)
dyspepsia, N, V, indigestion, epigastric pain, gastritis, duodenitis, H pylori infection	105	(3.2)	1.9	107	(3.3)	1.9	0.99	(0.76, 1.29)	129	(2.4)	1.8	145	(2.7)	1.8	0.88	(0.70, 1.11)
tachycardia	102	(3.1)	1.9	160	(4.9)	2.9	0.64	(0.50, 0.82)	96	(1.8)	1.3	129	(2.4)	1.6	0.74	(0.57, 0.96)
solid neoplasia, ALL (benign, malignant, unknown)	96	(2.9)	1.8	83	(2.5)	1.5	1.16	(0.87, 1.55)	134	(2.4)	1.9	148	(2.7)	1.8	0.90	(0.71, 1.13)
phosphenes, visual brightness	91	(2.8)	1.7	18	(0.5)	0.3	5.08	(3.07, 8.40)	206	(3.8)	2.8	46	(0.8)	0.6	4.44	(3.23, 6.10)
gout, high uric acid	90	(2.8)	1.7	93	(2.8)	1.7	0.97	(0.73, 1.29)	91	(1.7)	1.3	99	(1.8)	1.2	0.91	(0.69, 1.21)
cerebral ischemia (stroke, ICH, TIA)	85	(2.6)	1.6	100	(3.1)	1.8	0.85	(0.64, 1.13)	124	(2.3)	1.7	122	(2.2)	1.5	1.01	(0.79, 1.29)
COPD, COPD exacerbation	81	(2.5)	1.5	88	(2.7)	1.6	0.93	(0.69, 1.25)	81	(1.5)	1.1	86	(1.6)	1.1	0.93	(0.69, 1.26)
Stroke, TIA	83	(2.5)	1.5	93	(2.8)	1.7	0.90	(0.67, 1.21)	113	(2.1)	1.6	120	(2.2)	1.5	0.93	(0.72, 1.20)
bleeding	75	(2.3)	1.4	68	(2.1)	1.2	1.11	(0.80, 1.54)	70	(1.3)	1.0	71	(1.3)	0.9	0.98	(0.71, 1.36)

	SHIFT								BEAUTIFUL							
	Ivabradine N=3260			Placebo N=3278					Ivabradine N=5477			Placebo N=5430				
Adverse events	**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**		**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**	
GOT, GPT, GGTP, LFTs	76	(2.3)	1.4	72	(2.2)	1.3	1.06	(0.77, 1.46)	66	(1.2)	0.9	87	(1.6)	1.1	0.75	(0.55, 1.03)
arthralgia, arthritis, arthrosis	74	(2.3)	1.4	79	(2.4)	1.4	0.94	(0.69, 1.29)	82	(1.5)	1.1	104	(1.9)	1.3	0.78	(0.59, 1.04)
influenza	67	(2.1)	1.2	70	(2.1)	1.3	0.96	(0.69, 1.34)	65	(1.2)	0.9	73	(1.3)	0.9	0.88	(0.63, 1.23)
diarrhea, colitis, enteritis, proctitis, gastroenteritis, C-diff	64	(2.0)	1.2	69	(2.1)	1.3	0.93	(0.66, 1.30)	109	(2.0)	1.5	97	(1.8)	1.2	1.11	(0.85, 1.46)
hypotension	65	(2.0)	1.2	88	(2.7)	1.6	0.74	(0.54, 1.02)	51	(0.9)	0.7	75	(1.4)	0.9	0.67	(0.47, 0.95)
AV block	61	(1.9)	1.1	52	(1.6)	0.9	1.18	(0.82, 1.70)	55	(1.0)	0.8	50	(0.9)	0.6	1.09	(0.74, 1.60)
VT	61	(1.9)	1.1	70	(2.1)	1.3	0.88	(0.63, 1.24)	53	(1.0)	0.7	73	(1.3)	0.9	0.72	(0.51, 1.02)
Stroke (ischemic hemorrhagic)	63	(1.9)	1.2	80	(2.4)	1.5	0.79	(0.57, 1.10)	89	(1.6)	1.2	93	(1.7)	1.1	0.95	(0.71, 1.27)
asthenia, fatigue, malaise, weakness, narcolepsy	60	(1.8)	1.1	38	(1.2)	0.7	1.59	(1.06, 2.38)	86	(1.6)	1.2	92	(1.7)	1.1	0.93	(0.69, 1.24)
UTI	60	(1.8)	1.1	81	(2.5)	1.5	0.74	(0.53, 1.03)	73	(1.3)	1.0	84	(1.5)	1.0	0.86	(0.63, 1.17)
dizziness, light-headedness	55	(1.7)	1.0	47	(1.4)	0.9	1.18	(0.80, 1.74)	104	(1.9)	1.4	88	(1.6)	1.1	1.17	(0.88, 1.55)
arteriosclerosis, vascular disease, PVD, bowel ischemia	56	(1.7)	1.0	66	(2.0)	1.2	0.85	(0.60, 1.21)	90	(1.6)	1.2	91	(1.7)	1.1	0.98	(0.73, 1.31)
cancer (non-squam cell)	52	(1.6)	1.0	48	(1.5)	0.9	1.09	(0.74, 1.61)	81	(1.5)	1.1	97	(1.8)	1.2	0.83	(0.62, 1.11)
cough	45	(1.4)	0.8	51	(1.6)	0.9	0.89	(0.60, 1.32)	53	(1.0)	0.7	61	(1.1)	0.7	0.86	(0.60, 1.24)
cholecystitis, cholelithiasis, bile duct stone	47	(1.4)	0.9	59	(1.8)	1.1	0.80	(0.55, 1.17)	59	(1.1)	0.8	58	(1.1)	0.7	1.01	(0.70, 1.45)
abdominal pain, distension, bloating, spasm, IBS, megacolon	47	(1.4)	0.9	60	(1.8)	1.1	0.79	(0.54, 1.15)	74	(1.4)	1.0	88	(1.6)	1.1	0.83	(0.61, 1.13)
headache	45	(1.4)	0.8	60	(1.8)	1.1	0.75	(0.51, 1.10)	57	(1.0)	0.8	56	(1.0)	0.7	1.01	(0.70, 1.46)
Fall	41	(1.3)	0.8	45	(1.4)	0.8	0.92	(0.60, 1.40)	5	(0.1)	0.1	4	(0.1)	0.0	1.24	(0.33, 4.62)
PACs	42	(1.3)	0.8	50	(1.5)	0.9	0.84	(0.56, 1.26)	39	(0.7)	0.5	27	(0.5)	0.3	1.43	(0.88, 2.33)

	SHIFT								BEAUTIFUL							
	Ivabradine N=3260			Placebo N=3278					Ivabradine N=5477			Placebo N=5430				
Adverse events	**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**		**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**	
Ischemic stroke	44	(1.3)	0.8	62	(1.9)	1.1	0.71	(0.48, 1.04)	49	(0.9)	0.7	54	(1.0)	0.7	0.90	(0.61, 1.32)
QRS prolonged, BBB	39	(1.2)	0.7	36	(1.1)	0.7	1.09	(0.69, 1.71)	32	(0.6)	0.4	53	(1.0)	0.7	0.60	(0.39, 0.93)
vertigo vestibular dysfunction	36	(1.1)	0.7	17	(0.5)	0.3	2.13	(1.20, 3.78)	53	(1.0)	0.7	53	(1.0)	0.7	0.99	(0.68, 1.45)
AFL	37	(1.1)	0.7	35	(1.1)	0.6	1.06	(0.67, 1.68)	55	(1.0)	0.8	48	(0.9)	0.6	1.14	(0.78, 1.68)
dyspnea, SOB	36	(1.1)	0.7	39	(1.2)	0.7	0.93	(0.59, 1.46)	79	(1.4)	1.1	72	(1.3)	0.9	1.09	(0.79, 1.50)
high K	37	(1.1)	0.7	62	(1.9)	1.1	0.60	(0.40, 0.90)	83	(1.5)	1.1	83	(1.5)	1.0	0.99	(0.73, 1.34)
gastric or duodenal ulcer, erosion, perforation	32	(1.0)	0.6	23	(0.7)	0.4	1.40	(0.82, 2.39)	31	(0.6)	0.4	35	(0.6)	0.4	0.88	(0.54, 1.42)
GI bleed	31	(1.0)	0.6	27	(0.8)	0.5	1.15	(0.69, 1.92)	27	(0.5)	0.4	32	(0.6)	0.4	0.84	(0.50, 1.40)
low K	34	(1.0)	0.6	32	(1.0)	0.6	1.07	(0.66, 1.73)	29	(0.5)	0.4	39	(0.7)	0.5	0.74	(0.46, 1.19)
hyper_hypo thyroid, thyroiditis, goiter	34	(1.0)	0.6	36	(1.1)	0.7	0.95	(0.60, 1.51)	31	(0.6)	0.4	42	(0.8)	0.5	0.73	(0.46, 1.16)
fracture	33	(1.0)	0.6	37	(1.1)	0.7	0.90	(0.56, 1.44)	43	(0.8)	0.6	55	(1.0)	0.7	0.78	(0.52, 1.16)
pre-syncope or syncope	34	(1.0)	0.6	49	(1.5)	0.9	0.70	(0.45, 1.08)	53	(1.0)	0.7	74	(1.4)	0.9	0.71	(0.50, 1.01)
syncope	34	(1.0)	0.6	49	(1.5)	0.9	0.70	(0.45, 1.08)	53	(1.0)	0.7	74	(1.4)	0.9	0.71	(0.50, 1.01)
stone, renal colic	28	(0.9)	0.5	20	(0.6)	0.4	1.41	(0.80, 2.50)	22	(0.4)	0.3	20	(0.4)	0.2	1.09	(0.60, 1.99)
gynecomastia	30	(0.9)	0.6	23	(0.7)	0.4	1.31	(0.76, 2.25)	10	(0.2)	0.1	12	(0.2)	0.1	0.83	(0.36, 1.92)
cataract	30	(0.9)	0.6	24	(0.7)	0.4	1.26	(0.74, 2.15)	36	(0.7)	0.5	44	(0.8)	0.5	0.81	(0.52, 1.26)
benign prostatic hypertrophy	29	(0.9)	0.5	24	(0.7)	0.4	1.22	(0.71, 2.09)	30	(0.5)	0.4	51	(0.9)	0.6	0.58	(0.37, 0.91)
palpitations	28	(0.9)	0.5	23	(0.7)	0.4	1.22	(0.70, 2.11)	21	(0.4)	0.3	32	(0.6)	0.4	0.65	(0.38, 1.13)
edema, non-pulm, fluid retention, overload	28	(0.9)	0.5	24	(0.7)	0.4	1.17	(0.68, 2.01)	45	(0.8)	0.6	63	(1.2)	0.8	0.71	(0.49, 1.04)
depression	30	(0.9)	0.6	29	(0.9)	0.5	1.04	(0.63, 1.73)	27	(0.5)	0.4	34	(0.6)	0.4	0.79	(0.48, 1.31)

	SHIFT								BEAUTIFUL							
	Ivabradine N=3260			Placebo N=3278					Ivabradine N=5477			Placebo N=5430				
Adverse events	**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**		**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**	
visual disturbance, corneal deposits	27	(0.8)	0.5	10	(0.3)	0.2	2.71	(1.31, 5.59)	60	(1.1)	0.8	38	(0.7)	0.5	1.57	(1.05, 2.35)
chest pain (not angina or unknown)	25	(0.8)	0.5	19	(0.6)	0.3	1.32	(0.73, 2.39)	75	(1.4)	1.0	95	(1.7)	1.2	0.78	(0.58, 1.05)
constipation	26	(0.8)	0.5	29	(0.9)	0.5	0.90	(0.53, 1.52)	27	(0.5)	0.4	24	(0.4)	0.3	1.12	(0.65, 1.94)
insomnia, sleep disturbance, abnormal dreams	26	(0.8)	0.5	31	(0.9)	0.6	0.84	(0.50, 1.41)	37	(0.7)	0.5	43	(0.8)	0.5	0.85	(0.55, 1.32)
anxiety, nervousness, panic attacks	25	(0.8)	0.5	34	(1.0)	0.6	0.74	(0.44, 1.24)	38	(0.7)	0.5	30	(0.6)	0.4	1.26	(0.78, 2.03)
VFib	24	(0.7)	0.4	12	(0.4)	0.2	2.01	(1.01, 4.01)	16	(0.3)	0.2	13	(0.2)	0.2	1.22	(0.59, 2.53)
orthostasis	24	(0.7)	0.4	14	(0.4)	0.3	1.72	(0.89, 3.32)	14	(0.3)	0.2	15	(0.3)	0.2	0.93	(0.45, 1.92)
cellulitis, erysipelas	24	(0.7)	0.4	21	(0.6)	0.4	1.15	(0.64, 2.06)	18	(0.3)	0.2	24	(0.4)	0.3	0.74	(0.40, 1.36)
infection, bacterial	23	(0.7)	0.4	28	(0.9)	0.5	0.83	(0.48, 1.44)	12	(0.2)	0.2	14	(0.3)	0.2	0.85	(0.39, 1.84)
high or third deg AV Block	18	(0.6)	0.3	6	(0.2)	0.1	3.02	(1.20, 7.60)	14	(0.3)	0.2	16	(0.3)	0.2	0.87	(0.43, 1.78)
TIA	21	(0.6)	0.4	13	(0.4)	0.2	1.62	(0.81, 3.23)	24	(0.4)	0.3	31	(0.6)	0.4	0.77	(0.45, 1.31)
weight gain	20	(0.6)	0.4	17	(0.5)	0.3	1.18	(0.62, 2.25)	18	(0.3)	0.2	13	(0.2)	0.2	1.37	(0.67, 2.79)
pulm edema	21	(0.6)	0.4	26	(0.8)	0.5	0.81	(0.46, 1.44)	.		.	.		.	.	
retinopathy, retinal disorders	19	(0.6)	0.4	28	(0.9)	0.5	0.68	(0.38, 1.22)	20	(0.4)	0.3	14	(0.3)	0.2	1.42	(0.72, 2.81)
pancreatitis	17	(0.5)	0.3	9	(0.3)	0.2	1.90	(0.85, 4.26)	13	(0.2)	0.2	14	(0.3)	0.2	0.92	(0.43, 1.96)
herpes virus	16	(0.5)	0.3	9	(0.3)	0.2	1.79	(0.79, 4.04)	20	(0.4)	0.3	21	(0.4)	0.3	0.94	(0.51, 1.73)
ecchymosis, hematoma, bruise	16	(0.5)	0.3	13	(0.4)	0.2	1.24	(0.60, 2.57)	12	(0.2)	0.2	7	(0.1)	0.1	1.70	(0.67, 4.31)
hepatitis	17	(0.5)	0.3	18	(0.5)	0.3	0.95	(0.49, 1.84)	8	(0.1)	0.1	14	(0.3)	0.2	0.57	(0.24, 1.36)
anuria, ARF	17	(0.5)	0.3	19	(0.6)	0.3	0.90	(0.47, 1.73)	21	(0.4)	0.3	12	(0.2)	0.1	1.73	(0.85, 3.51)
cardiogenic shock	15	(0.5)	0.3	17	(0.5)	0.3	0.89	(0.45, 1.78)	.		.	7	(0.1)	0.1	.	(., .)

	SHIFT								BEAUTIFUL							
	Ivabradine N=3260			Placebo N=3278					Ivabradine N=5477			Placebo N=5430				
Adverse events	**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**		**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**	
hernia	15	(0.5)	0.3	31	(0.9)	0.6	0.49	(0.27, 0.91)	31	(0.6)	0.4	44	(0.8)	0.5	0.70	(0.44, 1.11)
Myalgia, myositis, rhabdomyolysis	13	(0.4)	0.2	18	(0.5)	0.3	0.73	(0.36, 1.49)	29	(0.5)	0.4	19	(0.3)	0.2	1.51	(0.85, 2.69)
wheeze, bronchospasm, asthma	12	(0.4)	0.2	23	(0.7)	0.4	0.52	(0.26, 1.04)	15	(0.3)	0.2	26	(0.5)	0.3	0.57	(0.30, 1.07)
infection, fungal	12	(0.4)	0.2	25	(0.8)	0.5	0.48	(0.24, 0.95)	19	(0.3)	0.3	38	(0.7)	0.5	0.50	(0.29, 0.87)
rash, eruption	9	(0.3)	0.2	13	(0.4)	0.2	0.70	(0.30, 1.64)	25	(0.5)	0.3	26	(0.5)	0.3	0.95	(0.55, 1.64)
cardiac thrombus	11	(0.3)	0.2	21	(0.6)	0.4	0.53	(0.26, 1.10)	12	(0.2)	0.2	23	(0.4)	0.3	0.52	(0.26, 1.04)
pulmonary embolism	11	(0.3)	0.2	26	(0.8)	0.5	0.43	(0.21, 0.87)	13	(0.2)	0.2	13	(0.2)	0.2	0.99	(0.46, 2.13)
allergic RXN, hypersensitivity	8	(0.2)	0.1	19	(0.6)	0.3	0.42	(0.18, 0.96)	14	(0.3)	0.2	15	(0.3)	0.2	0.93	(0.45, 1.92)
confusion, delirium, altered mental status, disorientation, lethargy, somnolence, coma	2	(0.1)	0.0	10	(0.3)	0.2	0.20	(0.04, 0.91)	26	(0.5)	0.4	13	(0.2)	0.2	1.98	(1.02, 3.85)

Reviewer's analysis: bs\data\LD2d\create table cuts. Applicant's data: SHIFT, BEAUTIFUL\adve

Table 85. Preferred term adverse events occurring in ≥ 0.5% of subjects in either arm in SHIFT or BEAUTIFUL

	SHIFT								BEAUTIFUL							
	Ivabradine N=3260			Placebo N=3278					Ivabradine N=5477			Placebo N=5430				
Preferred term	**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**		**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**	
All	2416	(74.1)	44.5	2390	(72.9)	43.4	1.02	(0.99, 1.05)	3048	(55.7)	42.1	3016	(55.5)	37.0	--	--
Cardiac failure	703	(21.6)	13.0	844	(25.7)	15.3	0.84	(0.77, 0.92)	552	(10.1)	7.6	584	(10.8)	7.2	0.94	(0.84, 1.05)
Atrial fibrillation	268	(8.2)	4.9	216	(6.6)	3.9	1.25	(1.05, 1.49)	286	(5.2)	4.0	264	(4.9)	3.2	1.07	(0.91, 1.26)
Blood pressure inadequately controlled	228	(7.0)	4.2	198	(6.0)	3.6	1.16	(0.96, 1.39)	196	(3.6)	2.7	189	(3.5)	2.3	1.03	(0.85, 1.25)
Heart rate decreased	181	(5.6)	3.3	45	(1.4)	0.8	4.04	(2.93, 5.58)	171	(3.1)	2.4	34	(0.6)	0.4	4.99	(3.46, 7.20)
Bradycardia	148	(4.5)	2.7	28	(0.9)	0.5	5.31	(3.56, 7.93)	206	(3.8)	2.8	56	(1.0)	0.7	3.65	(2.72, 4.89)
Ventricular extrasystoles	144	(4.4)	2.7	138	(4.2)	2.5	1.05	(0.84, 1.32)	116	(2.1)	1.6	108	(2.0)	1.3	1.06	(0.82, 1.37)
Angina pectoris	134	(4.1)	2.5	141	(4.3)	2.6	0.96	(0.76, 1.21)	136	(2.5)	1.9	162	(3.0)	2.0	0.83	(0.66, 1.04)
Diabetes mellitus inadequate control	135	(4.1)	2.5	141	(4.3)	2.6	0.96	(0.76, 1.21)	170	(3.1)	2.3	192	(3.5)	2.4	0.88	(0.72, 1.08)
Pneumonia	121	(3.7)	2.2	131	(4.0)	2.4	0.93	(0.73, 1.19)	123	(2.2)	1.7	112	(2.1)	1.4	1.09	(0.85, 1.40)
Angina unstable	118	(3.6)	2.2	126	(3.8)	2.3	0.94	(0.73, 1.20)	155	(2.8)	2.1	202	(3.7)	2.5	0.76	(0.62, 0.93)
Sudden death	111	(3.4)	2.0	119	(3.6)	2.2	0.94	(0.73, 1.21)	204	(3.7)	2.8	185	(3.4)	2.3	1.09	(0.90, 1.33)
Anaemia	96	(2.9)	1.8	100	(3.1)	1.8	0.97	(0.74, 1.28)	68	(1.2)	0.9	69	(1.3)	0.8	0.98	(0.70, 1.37)
Phosphenes	89	(2.7)	1.6	16	(0.5)	0.3	5.59	(3.29, 9.50)	206	(3.8)	2.8	46	(0.8)	0.6	4.44	(3.23, 6.10)
Sudden cardiac death	73	(2.2)	1.3	68	(2.1)	1.2	1.08	(0.78, 1.50)	.		.	.		.	.	
Influenza	67	(2.1)	1.2	70	(2.1)	1.3	0.96	(0.69, 1.34)	65	(1.2)	0.9	73	(1.3)	0.9	0.88	(0.63, 1.23)
Bronchitis acute	68	(2.1)	1.3	85	(2.6)	1.5	0.80	(0.58, 1.10)	59	(1.1)	0.8	68	(1.3)	0.8	0.86	(0.61, 1.22)
Nasopharyngitis	66	(2.0)	1.2	70	(2.1)	1.3	0.95	(0.68, 1.33)	85	(1.6)	1.2	87	(1.6)	1.1	0.97	(0.72, 1.30)
Chronic obstructive pulmonary disease	65	(2.0)	1.2	78	(2.4)	1.4	0.84	(0.61, 1.16)	58	(1.1)	0.8	58	(1.1)	0.7	0.99	(0.69, 1.42)

	SHIFT								BEAUTIFUL							
	Ivabradine N=3260			Placebo N=3278					Ivabradine N=5477			Placebo N=5430				
Preferred term	**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**		**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**	
Acute myocardial infarction	63	(1.9)	1.2	53	(1.6)	1.0	1.20	(0.84, 1.72)	82	(1.5)	1.1	88	(1.6)	1.1	0.92	(0.68, 1.24)
Renal failure	63	(1.9)	1.2	83	(2.5)	1.5	0.76	(0.55, 1.05)	69	(1.3)	1.0	74	(1.4)	0.9	0.92	(0.66, 1.27)
Hypotension	63	(1.9)	1.2	86	(2.6)	1.6	0.74	(0.54, 1.02)	50	(0.9)	0.7	75	(1.4)	0.9	0.66	(0.46, 0.94)
Ventricular tachycardia	60	(1.8)	1.1	70	(2.1)	1.3	0.86	(0.61, 1.21)	53	(1.0)	0.7	73	(1.3)	0.9	0.72	(0.51, 1.02)
Blood creatinine increased	56	(1.7)	1.0	46	(1.4)	0.8	1.22	(0.83, 1.80)	58	(1.1)	0.8	54	(1.0)	0.7	1.06	(0.73, 1.53)
Dizziness	55	(1.7)	1.0	47	(1.4)	0.9	1.18	(0.80, 1.74)	104	(1.9)	1.4	87	(1.6)	1.1	1.19	(0.90, 1.58)
Myocardial infarction	57	(1.7)	1.1	51	(1.6)	0.9	1.12	(0.77, 1.63)	67	(1.2)	0.9	82	(1.5)	1.0	0.81	(0.59, 1.12)
Transaminases increased	46	(1.4)	0.8	42	(1.3)	0.8	1.10	(0.73, 1.67)	33	(0.6)	0.5	43	(0.8)	0.5	0.76	(0.48, 1.19)
Hyperuricaemia	47	(1.4)	0.9	52	(1.6)	0.9	0.91	(0.62, 1.35)	30	(0.5)	0.4	27	(0.5)	0.3	1.10	(0.65, 1.85)
Headache	45	(1.4)	0.8	57	(1.7)	1.0	0.79	(0.54, 1.16)	55	(1.0)	0.8	56	(1.0)	0.7	0.97	(0.67, 1.40)
Respiratory tract infection	44	(1.3)	0.8	32	(1.0)	0.6	1.38	(0.88, 2.17)	44	(0.8)	0.6	52	(1.0)	0.6	0.84	(0.56, 1.25)
Bronchitis	41	(1.3)	0.8	39	(1.2)	0.7	1.06	(0.69, 1.64)	77	(1.4)	1.1	90	(1.7)	1.1	0.85	(0.63, 1.15)
Cough	42	(1.3)	0.8	44	(1.3)	0.8	0.96	(0.63, 1.46)	49	(0.9)	0.7	52	(1.0)	0.6	0.93	(0.63, 1.37)
Fall	41	(1.3)	0.8	45	(1.4)	0.8	0.92	(0.60, 1.40)	5	(0.1)	0.1	4	(0.1)	0.0	1.24	(0.33, 4.62)
Supraventricular extrasystoles	41	(1.3)	0.8	50	(1.5)	0.9	0.82	(0.54, 1.24)	39	(0.7)	0.5	27	(0.5)	0.3	1.43	(0.88, 2.33)
Gastritis	38	(1.2)	0.7	40	(1.2)	0.7	0.96	(0.62, 1.49)	46	(0.8)	0.6	46	(0.8)	0.6	0.99	(0.66, 1.49)
Sinus tachycardia	40	(1.2)	0.7	102	(3.1)	1.9	0.39	(0.27, 0.56)	14	(0.3)	0.2	44	(0.8)	0.5	0.32	(0.18, 0.58)
Atrial flutter	37	(1.1)	0.7	35	(1.1)	0.6	1.06	(0.67, 1.68)	55	(1.0)	0.8	48	(0.9)	0.6	1.14	(0.78, 1.68)
Atrioventricular block first degree	35	(1.1)	0.6	37	(1.1)	0.7	0.95	(0.60, 1.50)	24	(0.4)	0.3	19	(0.3)	0.2	1.25	(0.69, 2.28)
Ischaemic stroke	35	(1.1)	0.6	47	(1.4)	0.9	0.75	(0.49, 1.16)	38	(0.7)	0.5	41	(0.8)	0.5	0.92	(0.59, 1.43)
Fatigue	31	(1.0)	0.6	21	(0.6)	0.4	1.48	(0.85, 2.57)	59	(1.1)	0.8	56	(1.0)	0.7	1.04	(0.72, 1.50)

	SHIFT								BEAUTIFUL							
	Ivabradine N=3260			Placebo N=3278					Ivabradine N=5477			Placebo N=5430				
Preferred term	**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**		**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**	
Hypokalaemia	33	(1.0)	0.6	26	(0.8)	0.5	1.28	(0.77, 2.14)	23	(0.4)	0.3	32	(0.6)	0.4	0.71	(0.42, 1.21)
Diabetes mellitus non-insulin-dependent	31	(1.0)	0.6	29	(0.9)	0.5	1.07	(0.65, 1.77)	12	(0.2)	0.2	15	(0.3)	0.2	0.79	(0.37, 1.69)
Hypercholesterolaemia	33	(1.0)	0.6	34	(1.0)	0.6	0.98	(0.61, 1.58)	20	(0.4)	0.3	21	(0.4)	0.3	0.94	(0.51, 1.73)
Diarrhoea	33	(1.0)	0.6	35	(1.1)	0.6	0.95	(0.59, 1.52)	58	(1.1)	0.8	50	(0.9)	0.6	1.15	(0.79, 1.68)
Diabetes mellitus	34	(1.0)	0.6	37	(1.1)	0.7	0.92	(0.58, 1.46)	70	(1.3)	1.0	55	(1.0)	0.7	1.26	(0.89, 1.79)
Respiratory tract infection viral	31	(1.0)	0.6	35	(1.1)	0.6	0.89	(0.55, 1.44)	24	(0.4)	0.3	20	(0.4)	0.2	1.19	(0.66, 2.15)
Upper respiratory tract infection	34	(1.0)	0.6	54	(1.6)	1.0	0.63	(0.41, 0.96)	34	(0.6)	0.5	28	(0.5)	0.3	1.20	(0.73, 1.98)
Benign prostatic hyperplasia	29	(0.9)	0.5	23	(0.7)	0.4	1.27	(0.74, 2.19)	28	(0.5)	0.4	48	(0.9)	0.6	0.58	(0.36, 0.92)
Gynaecomastia	29	(0.9)	0.5	23	(0.7)	0.4	1.27	(0.74, 2.19)	10	(0.2)	0.1	12	(0.2)	0.1	0.83	(0.36, 1.92)
Hypertriglyceridaemia	28	(0.9)	0.5	23	(0.7)	0.4	1.22	(0.70, 2.11)	30	(0.5)	0.4	46	(0.8)	0.6	0.65	(0.41, 1.03)
Palpitations	28	(0.9)	0.5	23	(0.7)	0.4	1.22	(0.70, 2.11)	21	(0.4)	0.3	32	(0.6)	0.4	0.65	(0.38, 1.13)
Cataract	28	(0.9)	0.5	24	(0.7)	0.4	1.17	(0.68, 2.01)	36	(0.7)	0.5	44	(0.8)	0.5	0.81	(0.52, 1.26)
Back pain	28	(0.9)	0.5	27	(0.8)	0.5	1.04	(0.61, 1.76)	44	(0.8)	0.6	38	(0.7)	0.5	1.15	(0.75, 1.77)
Cardiovascular evaluation	28	(0.9)	0.5	28	(0.9)	0.5	1.01	(0.60, 1.70)	3	(0.1)	0.0	7	(0.1)	0.1	0.42	(0.11, 1.62)
Depression	29	(0.9)	0.5	29	(0.9)	0.5	1.01	(0.61, 1.69)	23	(0.4)	0.3	27	(0.5)	0.3	0.84	(0.48, 1.46)
Gout	29	(0.9)	0.5	30	(0.9)	0.5	0.97	(0.58, 1.61)	44	(0.8)	0.6	58	(1.1)	0.7	0.75	(0.51, 1.11)
Urinary tract infection	28	(0.9)	0.5	41	(1.3)	0.7	0.69	(0.43, 1.11)	41	(0.7)	0.6	49	(0.9)	0.6	0.83	(0.55, 1.25)
Renal failure chronic	29	(0.9)	0.5	49	(1.5)	0.9	0.60	(0.38, 0.95)	28	(0.5)	0.4	22	(0.4)	0.3	1.26	(0.72, 2.20)
Hyperkalaemia	29	(0.9)	0.5	56	(1.7)	1.0	0.52	(0.33, 0.81)	61	(1.1)	0.8	67	(1.2)	0.8	0.90	(0.64, 1.27)
Arteriogram coronary	26	(0.8)	0.5	13	(0.4)	0.2	2.01	(1.03, 3.90)	27	(0.5)	0.4	29	(0.5)	0.4	0.92	(0.55, 1.55)
Spinal osteoarthritis	26	(0.8)	0.5	21	(0.6)	0.4	1.24	(0.70, 2.20)	20	(0.4)	0.3	23	(0.4)	0.3	0.86	(0.47, 1.56)

	SHIFT								BEAUTIFUL							
	Ivabradine N=3260			Placebo N=3278					Ivabradine N=5477			Placebo N=5430				
Preferred term	**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**		**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**	
Oedema peripheral	25	(0.8)	0.5	23	(0.7)	0.4	1.09	(0.62, 1.92)	42	(0.8)	0.6	56	(1.0)	0.7	0.74	(0.50, 1.10)
Hypertension	27	(0.8)	0.5	26	(0.8)	0.5	1.04	(0.61, 1.78)	29	(0.5)	0.4	32	(0.6)	0.4	0.90	(0.55, 1.49)
Constipation	26	(0.8)	0.5	29	(0.9)	0.5	0.90	(0.53, 1.52)	27	(0.5)	0.4	24	(0.4)	0.3	1.12	(0.65, 1.94)
Peripheral arterial occlusive disease	27	(0.8)	0.5	32	(1.0)	0.6	0.85	(0.51, 1.42)	52	(0.9)	0.7	48	(0.9)	0.6	1.07	(0.72, 1.58)
Hypertensive crisis	27	(0.8)	0.5	33	(1.0)	0.6	0.82	(0.49, 1.36)	26	(0.5)	0.4	27	(0.5)	0.3	0.95	(0.56, 1.63)
Syncope	27	(0.8)	0.5	39	(1.2)	0.7	0.70	(0.43, 1.14)	43	(0.8)	0.6	54	(1.0)	0.7	0.79	(0.53, 1.18)
Osteoarthritis	27	(0.8)	0.5	45	(1.4)	0.8	0.60	(0.37, 0.96)	45	(0.8)	0.6	40	(0.7)	0.5	1.12	(0.73, 1.71)
Ventricular fibrillation	24	(0.7)	0.4	12	(0.4)	0.2	2.01	(1.01, 4.01)	16	(0.3)	0.2	13	(0.2)	0.2	1.22	(0.59, 2.53)
Asthenia	24	(0.7)	0.4	15	(0.5)	0.3	1.61	(0.85, 3.06)	16	(0.3)	0.2	23	(0.4)	0.3	0.69	(0.36, 1.30)
Bundle branch block left	23	(0.7)	0.4	20	(0.6)	0.4	1.16	(0.64, 2.11)	18	(0.3)	0.2	34	(0.6)	0.4	0.52	(0.29, 0.92)
Cholelithiasis	24	(0.7)	0.4	30	(0.9)	0.5	0.80	(0.47, 1.37)	30	(0.5)	0.4	30	(0.6)	0.4	0.99	(0.60, 1.64)
Orthostatic hypotension	20	(0.6)	0.4	9	(0.3)	0.2	2.23	(1.02, 4.89)	11	(0.2)	0.2	12	(0.2)	0.1	0.91	(0.40, 2.06)
Vertigo	21	(0.6)	0.4	11	(0.3)	0.2	1.92	(0.93, 3.98)	37	(0.7)	0.5	39	(0.7)	0.5	0.94	(0.60, 1.47)
Nausea	20	(0.6)	0.4	12	(0.4)	0.2	1.68	(0.82, 3.43)	30	(0.5)	0.4	28	(0.5)	0.3	1.06	(0.63, 1.77)
Transient ischaemic attack	21	(0.6)	0.4	13	(0.4)	0.2	1.62	(0.81, 3.23)	24	(0.4)	0.3	31	(0.6)	0.4	0.77	(0.45, 1.31)
Dyspepsia	21	(0.6)	0.4	17	(0.5)	0.3	1.24	(0.66, 2.35)	22	(0.4)	0.3	29	(0.5)	0.4	0.75	(0.43, 1.30)
Hyperglycaemia	19	(0.6)	0.4	17	(0.5)	0.3	1.12	(0.58, 2.15)	1	(0.0)	0.0	1	(0.0)	0.0	0.99	(0.06, 15.82)
Dyspnoea	20	(0.6)	0.4	21	(0.6)	0.4	0.96	(0.52, 1.77)	53	(1.0)	0.7	55	(1.0)	0.7	0.96	(0.66, 1.40)
Cardiac failure congestive	21	(0.6)	0.4	25	(0.8)	0.5	0.84	(0.47, 1.50)	.		.	1	(0.0)	0.0	.	(., .)
Acute pulmonary oedema	20	(0.6)	0.4	25	(0.8)	0.5	0.80	(0.45, 1.44)	.		.	.		.	.	

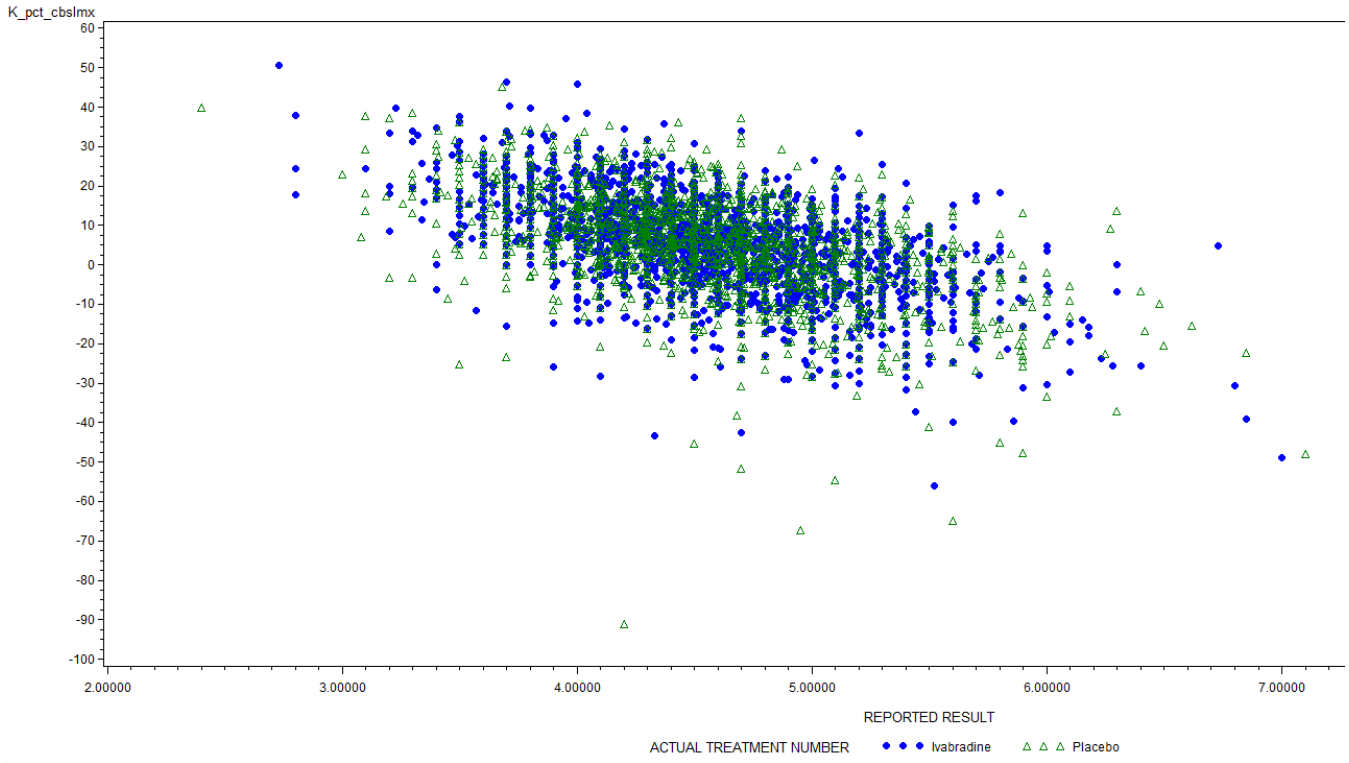
	SHIFT								BEAUTIFUL							
	Ivabradine N=3260			Placebo N=3278					Ivabradine N=5477			Placebo N=5430				
Preferred term	**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**		**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**	
Anxiety	20	(0.6)	0.4	25	(0.8)	0.5	0.80	(0.45, 1.44)	26	(0.5)	0.4	21	(0.4)	0.3	1.23	(0.69, 2.18)
Insomnia	20	(0.6)	0.4	25	(0.8)	0.5	0.80	(0.45, 1.44)	31	(0.6)	0.4	32	(0.6)	0.4	0.96	(0.59, 1.57)
Cardiac resynchronisation therapy	21	(0.6)	0.4	29	(0.9)	0.5	0.73	(0.42, 1.28)	2	(0.0)	0.0	1	(0.0)	0.0	1.98	(0.18, 21.83)
Hyperlipidaemia	21	(0.6)	0.4	32	(1.0)	0.6	0.66	(0.38, 1.14)	2	(0.0)	0.0	8	(0.1)	0.1	0.25	(0.05, 1.18)
Vision blurred	17	(0.5)	0.3	7	(0.2)	0.1	2.44	(1.01, 5.88)	54	(1.0)	0.7	31	(0.6)	0.4	1.73	(1.11, 2.69)
Arthralgia	16	(0.5)	0.3	7	(0.2)	0.1	2.30	(0.95, 5.58)	16	(0.3)	0.2	31	(0.6)	0.4	0.51	(0.28, 0.93)
Nephrolithiasis	16	(0.5)	0.3	10	(0.3)	0.2	1.61	(0.73, 3.54)	11	(0.2)	0.2	8	(0.1)	0.1	1.36	(0.55, 3.38)
Atrioventricular block second degree	15	(0.5)	0.3	12	(0.4)	0.2	1.26	(0.59, 2.69)	17	(0.3)	0.2	14	(0.3)	0.2	1.20	(0.59, 2.43)
Epistaxis	17	(0.5)	0.3	14	(0.4)	0.3	1.22	(0.60, 2.47)	17	(0.3)	0.2	24	(0.4)	0.3	0.70	(0.38, 1.30)
Dermatitis allergic	17	(0.5)	0.3	15	(0.5)	0.3	1.14	(0.57, 2.28)	19	(0.3)	0.3	16	(0.3)	0.2	1.18	(0.61, 2.29)
Erysipelas	15	(0.5)	0.3	14	(0.4)	0.3	1.08	(0.52, 2.23)	9	(0.2)	0.1	13	(0.2)	0.2	0.69	(0.30, 1.61)
Blood cholesterol increased	17	(0.5)	0.3	17	(0.5)	0.3	1.01	(0.52, 1.97)	56	(1.0)	0.8	75	(1.4)	0.9	0.74	(0.52, 1.04)
Cerebrovascular accident	15	(0.5)	0.3	16	(0.5)	0.3	0.94	(0.47, 1.90)	40	(0.7)	0.6	37	(0.7)	0.5	1.07	(0.69, 1.67)
Cardiogenic shock	15	(0.5)	0.3	17	(0.5)	0.3	0.89	(0.45, 1.78)	.		.	7	(0.1)	0.1	.	(., .)
Implantable defibrillator insertion	17	(0.5)	0.3	21	(0.6)	0.4	0.81	(0.43, 1.53)	12	(0.2)	0.2	15	(0.3)	0.2	0.79	(0.37, 1.69)
Renal failure acute	15	(0.5)	0.3	19	(0.6)	0.3	0.79	(0.40, 1.55)	21	(0.4)	0.3	12	(0.2)	0.1	1.73	(0.85, 3.51)
Diabetic neuropathy	16	(0.5)	0.3	24	(0.7)	0.4	0.67	(0.36, 1.26)	18	(0.3)	0.2	21	(0.4)	0.3	0.85	(0.45, 1.59)
Musculoskeletal chest pain	16	(0.5)	0.3	24	(0.7)	0.4	0.67	(0.36, 1.26)	6	(0.1)	0.1	7	(0.1)	0.1	0.85	(0.29, 2.53)
Supraventricular tachycardia	15	(0.5)	0.3	24	(0.7)	0.4	0.63	(0.33, 1.20)	13	(0.2)	0.2	13	(0.2)	0.2	0.99	(0.46, 2.13)
Renal impairment	12	(0.4)	0.2	7	(0.2)	0.1	1.72	(0.68, 4.36)	26	(0.5)	0.4	19	(0.3)	0.2	1.36	(0.75, 2.45)

	SHIFT								BEAUTIFUL							
	Ivabradine N=3260			Placebo N=3278					Ivabradine N=5477			Placebo N=5430				
Preferred term	**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**		**n**	**%**	**%PY**	**n**	**%**	**%PY**	**RR (95% CI)**	
Pain in extremity	13	(0.4)	0.2	9	(0.3)	0.2	1.45	(0.62, 3.39)	25	(0.5)	0.3	27	(0.5)	0.3	0.92	(0.53, 1.58)
Myalgia	13	(0.4)	0.2	17	(0.5)	0.3	0.77	(0.37, 1.58)	25	(0.5)	0.3	15	(0.3)	0.2	1.65	(0.87, 3.13)
Gastroenteritis	12	(0.4)	0.2	19	(0.6)	0.3	0.64	(0.31, 1.32)	28	(0.5)	0.4	28	(0.5)	0.3	0.99	(0.59, 1.67)
Chest pain	11	(0.3)	0.2	8	(0.2)	0.1	1.38	(0.56, 3.43)	60	(1.1)	0.8	77	(1.4)	0.9	0.77	(0.55, 1.08)
Renal cyst	11	(0.3)	0.2	19	(0.6)	0.3	0.58	(0.28, 1.22)	8	(0.1)	0.1	12	(0.2)	0.1	0.66	(0.27, 1.61)
Blood glucose increased	11	(0.3)	0.2	23	(0.7)	0.4	0.48	(0.23, 0.98)	50	(0.9)	0.7	48	(0.9)	0.6	1.03	(0.69, 1.53)
Pulmonary embolism	11	(0.3)	0.2	26	(0.8)	0.5	0.43	(0.21, 0.87)	13	(0.2)	0.2	13	(0.2)	0.2	0.99	(0.46, 2.13)
Skin ulcer	5	(0.2)	0.1	20	(0.6)	0.4	0.25	(0.09, 0.67)	6	(0.1)	0.1	15	(0.3)	0.2	0.40	(0.16, 1.03)
Death	4	(0.1)	0.1	1	(0.0)	0.0	4.02	(0.45, 35.95)	37	(0.7)	0.5	26	(0.5)	0.3	1.41	(0.86, 2.33)
Blood triglycerides increased	4	(0.1)	0.1	4	(0.1)	0.1	1.01	(0.25, 4.04)	59	(1.1)	0.8	62	(1.1)	0.8	0.94	(0.66, 1.34)

Reviewer's analysis: bs\data\LD2d\create table all sponsor2. Applicant's data: SHIFT, BEAUTIFUL\adven

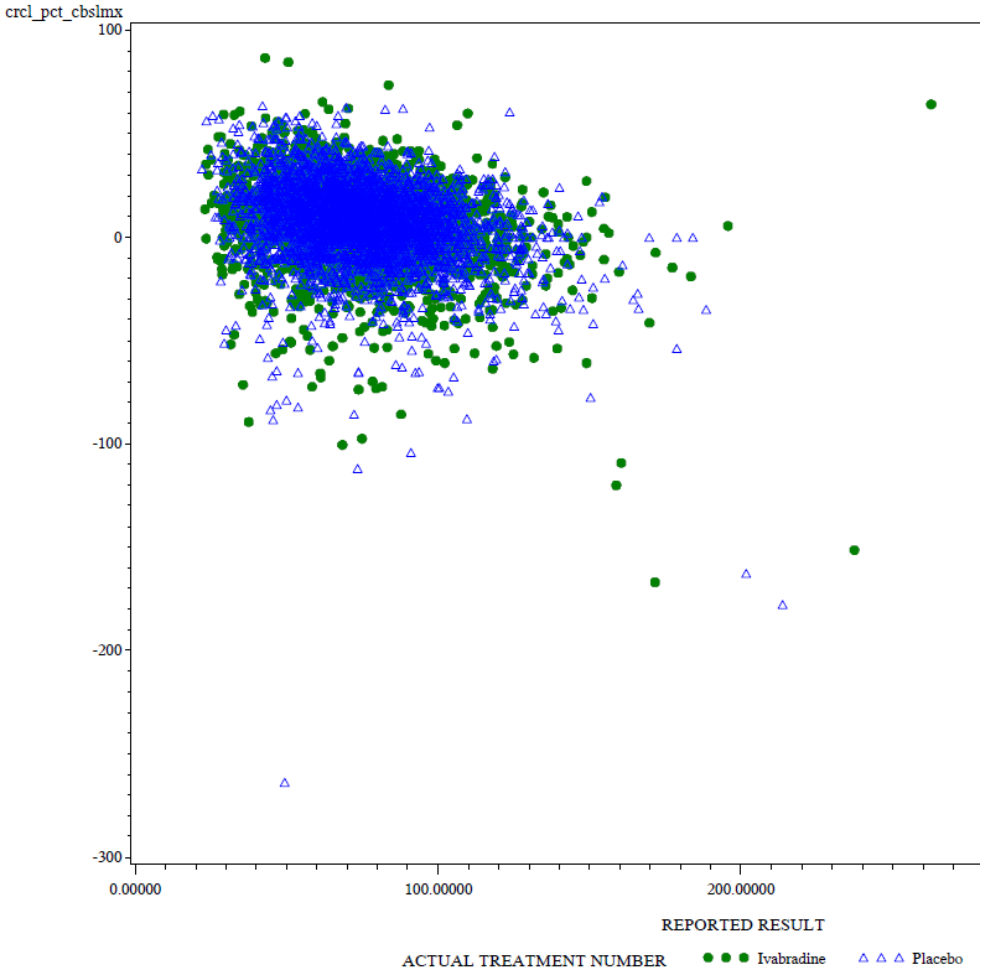
9.7 Laboratory figures

Figure 68. Baseline potassium vs. percent change in potassium - SHIFT



Reviewer's analysis. Note that ivabradine treatment is blue.

Figure 69. Baseline CrCL vs. percent change CrCL - SHIFT



Reviwer's analysis.

CrCL is GFR_{MDRD} per the formula below.

Creatinine clearance

GFR_{MDRD} = 186.3 x (creatinine *in µmol/L* / 88.4)$^{-1.154}$ x (age *in years*)$^{-0.203}$
x 1.212 if African American (ticked race = black in SHIFT)
x 0.742 if woman (**if male no correction factor**)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PRESTON M DUNNMON
12/04/2014

BACH N BEASLEY
12/04/2014

THOMAS A MARCINIAK
12/04/2014
Please see my CDTL review for a more complete discussion of efficacy.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 206143 **Applicant: Amgen** **Stamp Date: June 27, 2014**

Drug Name: Ivabradine **NDA/BLA Type: Priority**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	505(b)(1)			
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?			X	
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?			X	
15.	Describe the scientific bridge (e.g., BA/BE studies)			X	
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: CL3-16257-063 Study Title: Effects of ivabradine on cardiovascular events in patients with moderate to severe chronic heart failure and left ventricular systolic dysfunction: SHIFT study - A three-year randomized double-blind placebo-controlled international multicentre study Sample Size: 6558 total (randomized 1:1) Arms: 2 Location in submission: 5.3.5.1	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Yes Pivotal Study #1 SHIFT Indication: CHF Pivotal Study #2 Indication:	X			
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
22.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?		X		DCRP has requested CRFs from the BEAUTIFUL trial
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?		X		However, due diligence has been demonstrated in attempting to obtain this information
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- Inability to audit data from the two highest enrolling countries (Russia and Ukraine)
- SHIFT was conducted exclusively outside of the United States, not under an IND, and so US financial disclosure information was not requested. Two years after SHFIT was completed, in 2012, an attempt was made to collect this information retrospectively. The response rate of these investigators over the 628 sites was low.
- The relevance of the efficacy data in a heart failure population with a mean LVEF of 29% in whom device therapy was discouraged by protocol exclusion criteria such that device mirrored OUS medical practice prior to 2010 calls into question the applicability of the efficacy results to the US population of HFrEF patients.

Reviewing Medical Officer Date

Clinical Team Leader Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PRESTON M DUNNMON
08/04/2014

THOMAS A MARCINIAK
08/05/2014